ROLE OF ADENOSINE DEAMINASE (ADA) IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS

Thesis submitted for partial fulfillment of
Master Degree in chest Diseases

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TABLE OF CONTENTS

SUBJECT	PAGE
LIST OF ABBREVIATIONS	
INTRODUCTION	**1**
REVIEW OF LITERATURE	
AIM OF WORK	**4**
TUBERCULOSIS	**5**
• **Definition**	**5**
• **Epidemiology**	**5**
• **Tuberculosis in Egypt**	**8**
• **Pathogenesis**	**9**
• **Pathology**	**11**
• **Immunology**	**12**
• **Diagnosis** ✓ **Clinical presentation** ✓ **Radiological diagnosis** ✓ **Bacteriological diagnosis** ✓ **Hematology and Biochemistry** ✓ **Pulmonary – Physiological changes** ✓ **Recent advances in diagnosis** ✓ **Serological diagnosis**	**14**
• **Tests to detect latent infection** ✓ **Tuberculin skin test**	**32**
• **Assessment of Activity**	**37**
• **Differential diagnosis of pulmonary tuberculosis**	**38**
• **Complications of tuberculosis**	**39**

SUBJECT	PAGE
• Management of pulmonary tuberculosis	42
• BCG Vaccination	58
1. ADENOSINE DEAMINASE ✓ Definition ✓ Catabolic pathway ✓ Distribution ✓ Properties ✓ Role of Adenosine deaminase ✓ ADA deficiency ✓ Increased ADA Activity	59
2. TUBERCULOSIS AND ADENOSINE DEAMINASE ✓ In Serum ✓ In Pericardial effusion ✓ In Cerebrospinal fluid ✓ In Pleural effusion ✓ In Ascitic fluid	70
SUBJECTS AND METHODS	78
RESULTS	85
DISCUSSION	109
SUMMARY,CONCLUSION AND RECOMMENDATIONS	117
REFERENCES	122
APPENDIXES	
الملخص العربى	

LIST OF ABBREVIATIONS

1.	**APRT**	**Adenine Phosphoribosyl Transferase**
2.	**ADA**	**Adenosine Deaminase**
3.	**AP**	**Adenosine Phosphorylase**
4.	**AFB**	**Acid-Fast Bacilli**
5.	**AIDs**	**Acquired Immunodeficiency Syndrome**
6.	**ARI**	**Annual Risk of Infection**
7.	**AS**	**Ammonium-Sulfate**
8.	**BALF**	**Bronco-Alveolar Lavage Fluid**
9.	**BCG**	**Bacillus Calmette-Guerin**
10.	**CSF**	**Cerebro - Spinal Fluid**
11.	**DNA**	**Deoxyribo nueclic acid**
12.	**DTH**	**Delayed Type Hypersensitivity**
13.	**DOTS**	**Direct Observed Treatment with Short course chemotherapy**
14.	**ELISA**	**Enzyme-Linked Immunosorbent Assays**
15.	**E**	**Ethambutol**
16.	**H**	**Isoniazid**
17.	**HIO**	**Health Insurance Organization**
18.	**HRCT**	**High Resolution Computed Tomography**
19.	**HIV**	**Human Immunodeficiency Virus**
20.	**HGPRT**	**Hypoxanthine –Guanine Phosphoribosyl Transferase.**
21.	**HPLC**	**High Performance Liquid Chromatography**
22.	**IDUS**	**Injecting Drug Users**
23.	**IU**	**The International Unit**
24.	**IUATLD**	**International Union Against Tuberculosis and Lung Disease**
25.	**Kda**	**Kilodalton**
26.	**L J**	**Lowenstein-Jensen**
27.	**MIC**	**Minimal Inhibitory Concentration**
28.	**MDR**	**Multi-Drug Resistance**
29.	**MPT**	**Multiple Puncture Technique**
30.	**MOHP**	**Ministry Of Health and Population**
31.	**MOTT**	**Mycobacteria Other Than Tuberculosis**
32.	**MTB**	**Mycobacterium Tuberculosis**
33.	**NTP**	**National Tuberculosis Control Programme**
34.	**NTM**	**Non-Tuberculous Mycobacteria**
35.	**NAA**	**Nucleic Acid Amplification**

36.	**NAP**	**P-nitro α – acetyl Mino β- hydroxy propiophenone**
37.	**OT**	**Old Tuberculin**
38.	**PASA**	**Para Amino salicylic Acid**
39.	**PCR**	**Polymerase Chain Reaction**
40.	**PNP**	**Purine Nuclioside Phosphorylase**
41.	**PPD**	**Purified Protein Derivative**
42.	**R**	**Rifampicin**
43.	**RIA**	**Radioimmunoassay**
44.	**S**	**Streptomycin**
45.	**TB**	**Tuberculous Bacilli**
46.	**TCA**	**Trichloroacetic Acid**
47.	**USA**	**United State of America**
48.	**WHO**	**World Health Organization**
49.	**ZN**	**Ziehl-Nielsen**
50.	**Z**	**Pyrazinamide**

INTRODUCTION

Tuberculosis is a chronic granulomatous disease caused by *Mycobacterium tuberculosis* with various manifestations, involving most commonly the lung but all other systems as well. It is a reemergent killer, threatening a large population all over the world. ***(Raviglione et al., 1995)***

The World Health Organization recently estimated that between 1980 and 2005, 90 million TB patients were registered in national surveillance systems and reported to WHO, and more than 26 million were notified by DOTS programmes since 1995 and 2.6 to 2.9 million deaths from this disease occur annually around the world. ***(WHO Global Report 2007).***

The problem in diagnosing of tuberculosis is that no symptom or sign is exactly typical of it. The presence of infection in the body does not necessarily mean disease. From the disease point of view, recovering the bacilli from patient's specimen (by smear/culture) is specific but not sensitive. ***(Berger and Mejia, 1973).***

Tuberculosis has become the most important communicable disease in the world, with over 8 million cases of pulmonary tuberculosis occurring each year, 95% of which are in developing countries ***(Anon, 1991,).***

As tuberculosis has declined in the developed world, there has been an associated decrease in experience and awareness of the disease, as reflected by increasing numbers of diagnosis of tuberculosis made after, rather than before death. ***(Horne NW, 1984).***

Introduction

A Rapid and accurate diagnosis of symptomatic patients is a cornerstone of global tuberculosis control strategies. Remarkable progress has recently been made upgrading the speed and quality of mycobacteriology diagnostic services in developed countries, but for most of the world where T.B is a large public health burden those gains are still unrealized. Deficiencies in current case-finding tools in disease endemic countries have made it difficult to ensure access to good diagnostics at all health service levels, leaving many patients undiagnosed. Additionally, in well-established TB control programs where diagnostic access has been ensured, efforts to interrupt disease transmission have been hampered by the insensitivity and late detection of smear microscopy. **(Greenbaum M , 1980)**

A presumptive diagnosis of tuberculosis is usually based on clinical suspicious , chest radiography , skin test, examination of sputum or other body fluid for acid fast bacilli (AFB) and, possibly, histologic findings in a biopsy of infected tissue . A definitive diagnosis requires isolation of M.tuberculosis on culture. (***Sibibovsky R., 1994).***

Adenosine deaminase, ADA (Adenosine aminohydrolase, EC 3.5.3.3) specially reacts with adenosine and several adenines nucleoside analogues. The enzyme is widely distributed in animal tissues.The ADA assay may be used in adjunction with other methods in the diagnosis and follow up of tuberculosis with high sensitivity, specificity and ease in applicability and specimen collection ***(Canbolat O. et al, 1999).***

The enzyme level in serum increases in patients with different types of malignant tumours, but various workers do not agree upon the proportion of patients with leukemia and tumours having high ADA concentration in serum.

Introduction

Serum ADA level is valuable in identifying those patients in whom the diagnosis of pulmonary T.B should be actively considered. ***(Lakshmiv et al, 1992).***

Patients with pulmonary tuberculosis had significantly higher ADA activity in BALF than patients with non- tuberculosis lung diseases (P< 0.001). High Broncho-alveolar lavage fluid (BALF) ADA activity in pulmonary tuberculous patients suggests increased local production, in contrast, in those patients BALF lysozyme level is not significantly higher than in patients with interstitial lung diseases, so BALF ADA activity seems to be useful tool in the differentiation of tuberculosis from other lung diseases. ***(Orphanidou et al, 1998).***

ADA serum levels were statistically significantly increased in T.B patients when compared to lung cancer. ***(Kelbelc et al, 1995).***

Serum ADA levels in patients with pulmonary tuberculosis decrease during the initial months of effective treatment, perhaps this decrease might reflect the normalization of altered lymphocytes turnover induced by T.B ***(Collazos, et al, 1998).***

TUBERCULOSIS

Tuberculosis is a chronic granulomatous disease caused by Mycobacterium tuberculosis with various manifestations, involving most commonly the lung but all other systems as well. It is a reemergent killer, threatening a large population all over the world. The World Health Organization recently estimated 8.8 million new TB cases in 2005, 7.4 million in Asia and sub-Saharan Africa. A total of 1.6 million people died of TB, including 195 000 patients infected with HIV.

TB prevalence and death rates have probably been falling globally for several years. In 2005, the TB incidence rate was stable or in decline in all six WHO regions, and had reached a peak worldwide. However, the total number of new TB cases was still rising slowly, because the case-load continued to grow in the African, Eastern Mediterranean and South-East Asia regions.**(WHO Global Report, 2007)**

EPIDEMIOLOGY OF TUBERCULOSIS

In spite of major advances in diagnosis, treatment and prevention of tuberculosis (TB), the disease still constitutes a major health problem throughout the world. (***National Tuberculosis Control Programme of Egypt, 2004)***

Global burden of tuberculosis

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global emergency and in 1996, South Africa declared TB as a priority disease. The most effective means of controlling TB is

through rapid diagnosis by direct sputum microscopy for acid fast bacilli (AFB), or culture for Mycobacterium tuberculosis (MTB) and prompt initiation of the correct therapy by means of the Directly Observed Treatment, Short Course (DOTS) strategy.

In 1997, it was estimated that 10 million of the 30 million people infected with the human immuno-deficiency virus (HIV) worldwide were co-infected with TB. This review article focuses on TB diagnosis, including newer laboratory tests, treatment, and chemoprophylaxis. Special issues such as extra pulmonary TB, childhood TB, BCG immunization, and the deadly alliance between TB and HIV/AIDS are also considered. Tuberculosis is a treatable disease and the aim of any family practitioner should be to treat smear positive patients as soon as possible, and cure them at the first attempt**. *(*NO Ndjeka ,*2003)***

About one third of the world's population is infected by mycobacterium tuberculosis, which kills more people than any other single infectious agent. It is estimated by WHO that world wide in 1995 a total of nine million new cases of TB occurred and an estimated three million TB death, tuberculosis, poses a major problem for developing countries, as the following figures illustrate;

- Death from TB comprises 25 percent of all avoidable deaths in developing countries.
- 95 percent of all TB cases and 98 percent of TB death occur in developing countries.

- 75% percent of TB cases in developing countries are in the economically productive age group (15-50 years)
- The main reasons for the increase of global burden of TB are the following:
  - Inadequate health services.
  - Inadequate management practices resulting in poor case detection, diagnosis and treatment.
  - Demographic changes: increasing world population and changing age structure.

Size of the TB problem and its trend:

The size of TB problem can be measured through morbidity and mortality parameters.

Measuring morbidity:

- Prevalence of tuberculous infection, tuberculin infection rate (Tuberculin test for the non- BCG vaccinated) ;
- Prevalence of persons excreting TB bacilli (measuring smear positive cases) ;
- Notification of new cases with smear- positive pulmonary tuberculosis;
- Prevalence of tuberculosis disease;
- Age distribution of new TB cases;
- Level of anti-TB drug resistance, particularly Multi-Drug Resistance (MDR) among new TB cases ***(National Tuberculosis Programme of Egypt, 1998).***

Measuring mortality:

Rate of mortality from TB.

Some of these parameters are impractical to measure for example; in order to measure the prevalence of persons with pulmonary x-ray shadows it is necessary to regularly screen entire population. Likewise, the rate of mortality from TB is not effective. Anti-tuberculous drugs have reduced mortality to very low levels.

TUBERCULOSIS IN EGYPT

The current case detection rate for new sputum smear- positive TB cases in area covered by the National Tuberculosis Control Programme (NTP) is, on average, 14 per 100,000 populations.

In 1997, a total of 5,500 new sputum smears positive TB case were notified. Taking the most recent annual risk of infection (ARI) into consideration, this figure means that approximately 55% of all new smear positive TB cases detected through the ministry of health and population (MOHP) facilities. This figure excludes TB cases detected through health insurance organization (HIO), universities, private sector and other sectors involved in TB control.

In early 1997 a success rate of 72 percent was achieved in the treatment outcome of new sputum smear positive TB cases (cure and treatment complete rates combined). In areas where the Direct Observed

Treatment with short course chemotherapy (DOTS) strategy is implemented, the success rate reached 90 percent. ***(National Tuberculosis Control Programme of Egypt, 1998).***

In 2004, a total of 5,383 new sputum smears positive TB case were notified. Taking the most recent estimated annual risk of infection (ARI) by WHO in 2003 into consideration; this figure means that approximately 58% of all new smear positive TB cases detected through the ministry of health and population (MOHP) facilities. Include cases detected through health insurance organization (HIO), some universities, private sector and other sectors involved in TB control. With success rate of treatment is 89 %.***(National Tuberculosis Control Programme of Egypt, 2004).***

PATHOGENESIS OF TUBERCULOSIS

THE CAUSATIVE ORGANISM (TUBERCLE BACILLI):

Koch first described the tubercle bacillus now known as mycobacterium tuberculosis in 1882 ***(Koch R., 1932)***

Mycobacteria are now known to comprise a large group of acid fast, alcohol fast, aerobic or microaerophilic, non spore- forming, non-motile bacilli ***(David ., 1976)***

Tubercle bacilli are difficult to stain but once stained they strongly retain the dye, which is not removed by acid- alcohol solution. This acid and alcohol fastness can be demonstrated by the Ziehl-Nielsen staining procedure, of which there are various modifications. ***(Crofton and Doglous , 2000)***

In culture tubercle bacilli grow slowly, taking 2-6 weeks to form colonies on egg (e.g. Lowenstein-Jensen medium) and oleic acid-albumin agar media. Growth is optimal at temperature of 33-39◌ c at PH 6.5 – 6.8 in an atmosphere of 5 – 10% Co2 ***(Dannerberg A.M., 1994)***

In stained smears of pathological material, M.tuberculosis is seen as slightly bent roods, 2 - 4 µm length and 0.2 – 0 .5 µm wide which may be evenly stained or beaded and granular. On solid or liquid media the bacteria tend to be parallel and form long threads or cords ***(Dannerberg A.M., 1994)***

TRANSMISSION:

For many years tuberculosis was thought to be transmitted genetically. It is now known that infection is transmitted by the airborne route and that the unit of infection is a small particle called a droplet nucleus. The smaller particles were deposited on the alveolar surface, whereas the larger particles impacted in large airways and were cleared by mucociliary transport mechanisms. ***(Ratcliffe HL, and Palladino, 1953).***

It was postulated that airborne tuberculosis develops in humans by inhalation of a single bacillus contained in a droplet nucleus. Coughing, spitting, sneezing, singing and other respiratory maneuvers generate droplet nuclei due to evaporation of small respiratory droplets. These droplet, nuclei are dispersed throughout space without settling and the organisms that they contain can remain viable for extended periods of time. ***(Bass et al., 1995).***

Tenacious sputum may be more infectious than watery sputum. Most physicians consider, on the basis of these findings that after 1 or 2 weeks of effective chemotherapy the risk of transmission of tuberculosis is minimal, even from a smear- positive patient. ***(Riley RL, and Moodie AS, 1974 and Rouillon A.,et al, 1976)***

PATHOLOGY OF TUBERCULOSIS

Deposition of tubercle bacilli in the alveoli of the lungs is followed by vasodilatation and an influx of polymorph nuclear leucocytes and macrophages to the area. After several weeks the polymorph numbers diminish and macrophages predominate. The macrophages develop pale foamy cytoplasm rich lipid and crowd together as epithelioid cells to form the tubercle.

Some mononuclear cells fuse to form langrhans' giant cell lymphocytes surround the outer margin of the tubercle and in the center of the lesion a zone of caseous necrosis may appear that may subsequently calcify and is called Ghon's focus. This may be drained via lymphatics to hilar lymph nodes to form primary complex. ***(Balasubramanian V., et al, 1994)***

Most primary infection heals with or without calcification of the primary complex. Hematogenous spread may occur resulting in the seeding of tubercle bacilli to other parts of the lung as well as other organs.

Reactivated pulmonary tuberculosis is most often seen in the upper lung zones, most frequently to the posterior segment of the upper lobe or the apex of the lower lobe. The high ventilation- perfusion ratios, with alveolar PO_2 elevated relative to other zones is believed to reactivation at these sites. ***(Crompton G.R and McHordly G.L.R; 1989)***

Proliferation of tubercle bacilli in the caseous is followed by softening and liquefaction of the caseous material, which may discharge, into a bronchus with resultant cavity formation. ***(Crofton , 2000)***

Hemorrhage may result from extension of the caseous process into vessels within the cavity walls. Spread of caseous and liquefied material through the bronchial tree may disseminate the infection to other lung zones with or without the development of vigorous inflammatory exudates or tuberculous pneumonia ***(Crofton , 2000)***

Rupture of caseous pulmonary focus into a blood vessel may result in miliary tuberculosis

Rupture of caseous glands into trachea or major bronchi cause collapse of lung or even sudden death by suffocation in young children

IMMUNOLOGY OF TUBERCULOSIS

Koch first described the reinfection phenomenon that still bears his name ***(Koch R., 1890)***

Primary infection in guinea- pig skin was associated with a slowly progressive, well- localized, granulomatous response with lymph node involvement Subsequent infection with the same organism led to the development of an early localized indurated lesion that peaked at 72h followed by rapid healing. A similar secondary response could be induced in the skin of tuberculous patients by the intradermal injection of heat-killed tubercle bacilli or an extract of this organism (Tuberculin). ***(Dearborn E.; 1986)***

Immunity and hypersensitivity are now known to be mediated by a population of immunocompnent T-lymphocytes originated in the thymus- dependent area of spleen and lymph nodes ***(Mackaness GB, 1971)***

The immunity transferred by an initial infection is utilized in the form of vaccination with BCG which is derived form a virulent strain of M.bovis initially attenuated by cultivation on a potato-glycerin-bile medium for 230 serial transfers ***(Calmette A., 1936)***

A positive tuberculin test indicates the presence of hypersensitivity to tuberculin from either previous infection with tubercle

bacillus or from bacillus calmette-Guerin (BCG) vaccination**.** ***(WHO Tuberculosis Research Office, 1955)***

A weak reaction may be non- specific and indicate contact with other non- tuberculous environmental mycobacteria ***(Palmer CE, 1953)***

A strongly positive test in a child, who has not received BCG vaccination indicate an active disease, full anti-tuberculous treatment is required; if there is no evidence of active disease chemoprophylaxis is advisable. ***(American Thoracic Society, 1974)***

Negative tuberculin test makes active tuberculosis unlikely and indicates a lack of immunity so that BCG vaccination is recommended. ***(Comstok GW, et al, 1964).***

DIAGNOSIS OF PULMONARY TUBERCULOSIS:

A - CLINICAL PRESENTATION: -

A patient with pulmonary tuberculosis might remain for a long time asymptomatic and his lesion is only detected by radiological examination. On the other hand the patient may present with any of the following symptoms: (***Miller and MacGregor, 1978).***

Symptoms:

Symptoms may be divided into two categories: systemic and pulmonary.

1 - Systemic symptom: most frequently observed is a low grade fever, as a disease progresses, fever can be quite marked. Characteristically, the fever develops in the late afternoon and may not be accompanied by pronounced symptoms (e.g. night sweats) and other systemic manifestation of toxemia such as: malaise, irritability, weakness, unusual fatigue, and headache and weight loss.

2 - Pulmonary symptoms: start mainly with the development of caseation necrosis and concomitant liquefaction of the caseation, the patient will usually notice cough and expectoration, often associated with mild haemoptysis, chest pain is often localized and pleuritic; and shortness of breath usually indicates extensive disease with widespread involvement of the lungs and parenchyma or some form of tracheobronchial obstruction and therefore usually occurs late in the disease.

In miliary tuberculosis: the diagnosis can often be suspected at an earlier stage by the symptoms of progressive clinical deterioration, persistent pyrexia and splenomegaly ***(Rossman and Mayock, 1995).***

Signs:

Physical examination of the chest is usually of minimal help early in the disease, and frequently the findings are completely normal. The principal finding over areas of infiltration is one fine rales detected on deep inspiration followed by full expiration and hard, terminal cough, the so called post-tussive rales. They are usually detected in the apices of the lungs where reactivation disease is most common ***(Rossman and Mayock, 1995).***

Allergic manifestation may occur, including erythema nodosum and phlyctenular conjunctivitis. Erythema induratum (involvement of the lower leg and foot with redness, swelling and necrosis) probably represents a combination of local subcutaneous bacterial infection with an allergic response and should not be confused with erythema nodosum. The latter is due to circulating immune complexes, with resultant localized vascular damage ***(Rossman and Mayock, 1995)***

B - RADIOLOGICAL DIAGNOSIS:

A normal chest film almost, although not completely, excludes pulmonary tuberculosis.

Appearances suggestive of tuberculosis:

It is seldom possible to make completely confident diagnosis of pulmonary tuberculosis on radiological grounds alone, as almost all the manifestations of tuberculosis can be mimicked by other diseases; the following characteristics of a chest radiograph favour the diagnosis of tuberculosis:

* Opacities mainly in the upper zone (s);
* Patchy or nodular opacities;
* Presence of cavity or cavities;
* Presence of calcification;
* Bilateral opacities especially if in upper zones;
* Opacities that persist after several weeks (and thus are less likely due acute pneumonia).

Characteristic radiological appearance:-

- Soft confluent shadows alone suggest an exudative process and may be difficult to distinguish initially from a simple pneumonia.
- Linear shadows, especially if they produce distortion of fissures, trachea, mediastinum or diaphragm, suggest fibrosis;
- Bilateral upper zone fibrotic shadows, with shrinkage of the upper lobes and elevation pulmonary hila, are a common picture.
- The presence of calcification suggests healed disease.

Tuberculous disease is usually located in the posterior or apical segment of the upper lobe but, exceptionally, may be restricted to anterior segment of the upper lobe. ***(Spencer D. et al, 1990).***

Cavities in a mass of caseous material may initially have irregular walls that later become smoother and thinner as caseous material is coughed up or absorbed.

A cavity may become "blocked" and fill with purulent or caseous material, so called "tuberculoma".

The lymphadenopathy and pyrexia in the presence of a positive tuberculin test may be the only manifestations of tuberculous disease. ***(Farman DP and Spier WA; 1986).***

Radiological classification of disease extent:-

For clinical and research purposes, the classification of The National Tuberculosis Association of the USA has proved useful. ***(National Tuberculosis Association of USA, 1961).***

Minimal:

Minimal lesions include those that are of slight to moderate density but which do not contain demonstrable Cavitation. They may involve a small part of one or both lungs, but the total extent, regardless of distribution, should not exceed the volume of lung on one side that occupies the space above the second chostochondral junction and the spine of the fourth or the body of the fifth thoracic vertebra.

Moderately advanced:

Moderately advanced lesions may be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight to moderate density that may extent throughout the total lung volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one-third the volume of one lung; total diameter of cavitation; if present, must be less than 4 cm.

Far advanced:

Lesions more extensive than moderately advanced.

C- BACTERIOLOGICAL EXAMINATION:

1. SMEAR MICROSCOPY:

Sputum examination is of great value in making the diagnosis of pulmonary tuberculosis and in following the patient's response to treatment. If sputum production is difficult, it may be induced by inhalation of nebulized saline. Sputum should first examined by direct smear using the ziehl Nielsen stain. The fluorescence method allows large numbers of specimens to be examined rapidly**.** ***(Bandolier, 2000)***

Sputum smear examination is usually positive in advanced disease but may be negative in less advanced disease.

Sputum smear examination had a sensitivity of about 50% and a specificity of greater than 99% in two reported studies, with a positive predictive value of 91 – 98.5 %.***(Levy H.,et al 1989).***

In one study, smears were positive in 52% of patients with cavitating disease but in only 32% with non cavitating disease. ***(Greenbaum m., et al, 1980),*** the same study found that 96% of patients with cavitating disease had positive culture compared with only 70% with local infiltrates.

Sputum is sometimes both smear and culture negative even when there are well-marked radiological opacities, symptoms and subsequently appropriate response to anti-tuberculosis chemotherapy. Such patient may still demonstrate radiographic resolution following anti-tuberculosis chemotherapy consistent with the diagnosis. ***(Gorden FM., et al 1989).***

Following the initiation of modern chemotherapy, sputum cultures become negative most quickly in smear- positive disease, and least quickly in direct smear- positive disease, less quickly in direct smear positive cases with far advanced disease, where 80% still have positive cultures after 3 months of therapy. ***(Kim TC, et al, 1984).***

Bacteriological examination of samples other than sputum:

Gastric aspirate:

Sputum, especially if not abundant, is frequently swallowed rather than coughed up. In such a situation aspiration of early-morning gastric secretions may reveal acid-fast bacilli on staining, the secretions should be cultured***.(Cruickshank R.,1972).***

Laryngeal swabs:

Laryngeal swabs an alterative to gastric aspiration and are simpler to perform and less uncomfortable for the patient. ***(Pecora DV., 1959).***

The operator should be gowned and masked the swabs taken in pairs. The first swab usually makes the patient cough and the second often collected the better specimen.

Fiberoptic bronchoscopic specimens:

Where the conventional methods of obtaining bacterial confirmation of suspected tuberculosis have failed, flexible fiberoptic bronchoscopy may be utilized to provide direct smear or culture-positive specimens from bronchial washing, bronchial brushings or transbronchial biopsies. ***(*Abdel-Hakim et al 1995*)***

Trans-tracheal aspirate:

This procedure may also yield positive specimens when sputum are negative ***(Thadipalli H. ,et al, 1977)*** but other considers bronchoscopic specimens more productive of results.

Mediastinoscopy.

Occasionally, Mediastinoscopy may be necessary in patient to provide mediastinal lymph node specimens for pathological and bacteriological examination. ***(Cameron EWJ, 1978)***

2. CULTRURE AND IDENTIFICATION

(Small PM., 1994)

All clinical specimens suspected of containing mycobacteria should be inoculated (after appropriate digestion and decontamination, if required) onto culture media for two reasons:

(1) Culture is much more sensitive than microscopy, being able to detect as few as 10 bacteria/ml of digested, concentrated material;

(2) Growth of the organisms is necessary for precise species identification. Numerous mycobacterial culture media are available. Most of them fall into the two general categories, egg-potato-base media and agar-base media. Whenever possible, digested clinical specimens should be inoculated onto both kinds of media.

The most popular egg-based media are the Lowenstein-Jensen buffered egg-potato medium and the American Trudeau Society egg yolk-potato flour medium. Among the agar-based media, Middlebrook 7H-10, Middlebrook 7H-11, and Dubos oleic-albumin agar are recommended. Incubation of inoculated media in an atmosphere of 5 to 10% carbon

dioxide enhances both the number of positive isolations and the actual number of cultivable colonies. Whatever procedure is used, the time from the laboratory's receipt of the specimen to the clinician's receipt of the culture report is usually 3 to 6 week.

Mycobacterial growth observed on culture media should be quantified in some way. The following is a widely used scale:

No colonies	(negative)
Fewer than 50 colonies	Actual count
50-100 colonies	1+
100-200 colonies	2+
200-500 colonies (almost confluence)	3+
> 500 colonies (confluence)	4+

With the more refined culture methods available today and with the processing of multiple specimens from the same patient, it is not necessary for the clinical laboratory to resort to animal inoculation. In a few rare instances, guinea pig inoculation may be used when:

(1) Specimens are consistently contaminated on culture;

(2) Specimens are positive on microscopy but repeatedly negative on culture (untreated specimens should be injected);

(3) Specimens are aseptically collected where organisms may be few in number, and every attempt is made to establish the diagnosis of tuberculosis; and

(4) Small numbers of, M. tuberculosis are thought to be present in specimens known to contain other mycobacteria.

I-Conventional culture media:

A- Solid media

1- Agar – based

Middle- brooks 7H - 10

Middle – brook 7H – 11

Mitchison, P selective 7H – 11

2- Egg – based

Lowenstein – Jensen (L-J) with RNA

Lowenstein - Jensen (L-J) with pyruvic acid wallentein

B-Liquid media

Middle – brook 7 H broth

L-J glycerol medium is recommended for the isolation of the human type of tubercle bacillus whose growth is enhanced by glycerol, but bovine bacilli may be inhibited by glycerol and so may fail to grow on this medium. On the other hand, L.J medium with pyruvic acid increases the growth of M. bovis ***(Laid – L.M., 1989).***

Traditionally, the recognized techniques for identification of Mycobacteria have consisted of a combination of growth rate determination, pigment production, macroscopic colony, morphology and reaction to biochemical tests.

II - Radiometric Systems:

Perhaps the most widely used radiometric method to detect early growth of mycobacteria in culture is the BACTEC system, which employs a superscript 14 C-labeled substrate medium that is almost specific for mycobacteria. Since its introduction, the BACTEC method has provided more rapid growth (average, 9 days), specific identification

of M. tuberculosis (5 days), and rapid drug susceptibility testing (6 days). Although radiometric technology cannot replace completely the classic mycobacteriologic methods, and may underestimate drug resistance, this is a valuable new tool. Interfacing BACTEC (for more rapid growth) with techniques for rapid identification (e.g., genetic probes, high-pressure liquid chromatography, monoclonal antibodies) offers intriguing possibilities for future improvements in diagnosis. ***(Warren and Body, 1995).***

Radiometric systems can rapidly differentiate M. Tuberculosis from mycobacteria other than tuberculosis (MOTT) by testing for inhibition of growth in the presence of P-nitro α – acetyl a Mino β-hydroxy propiophenone (NAP). NAP is an intermediate compound in the synthesis of chloramphenicol that inhibit species in M. tuberculosis complex **(Zanetti S et al , 1997)**

D- HEMATOLOGY AND BIOCHEMISTRY.

White blood cell count.

In general, a normal total white blood count in the presence of extensive pulmonary shadowing on a chest radiograph favors a diagnosis of tuberculosis (or atypical pneumonia) rather than acute pneumonia or lung abscess.

Hemoglobin

A normochromic normocytic anemia is common in pulmonary tuberculosis but the more bizarre blood dyscrasias characteristic of miliary tuberculosis are unusual and, if present, most likely imply severe disease with cryptic miliary spread.

Liver function tests

It is not uncommon to find abnormalities of liver function tests in moderate or advanced tuberculosis. Since many of the chemotherapeutic agents are hepatotoxic, it is therefore important to determine baseline values for liver function before initiating chemotherapy.

E- RECENT ADVANCES IN DIAGNOSTICS.

For several decades, the field of clinical mycobacteriology remained rather stable. There were improvements in microscopy, refinements in digestion and decontamination methods, development of new tools for differential species identification, and application of numerical taxonomic methods. These resulted in sharpened capabilities to isolate mycobacteria from clinical specimens and to define the more than 50 species in the genus Mycobacterium. However, the long generation time of the mycobacteria and the multiplicity of time-consuming differential tests needed for species identification continued, until recently, to hamper the microbiologist. **(Morishita M, 1994)**

In contrast, during the 1980s, several new technologies were introduced and several older, established techniques were recalled to service, which have combined to revolutionize mycobacteriology. The application of many of these technologies is still in its infancy, but there are several that should make a dramatic impact on the speed and precision of clinical mycobacteriology in the coming years.

Genetic Probes

The use of genetic probe technologies offers tremendous promise in providing microbial identification at a variety of levels, family, genus, species, or subspecies. The most common probe technology is the single-stranded, radiolabeled DNA probe, now available commercially. Probes specific for the genus Mycobacterium, the M. tuberculosis complex (including M. tuberculosis, M. bovis, M. bovis BCG), M. africanum, and M. microti, and the two species M. avium and M. intracellular, are now available. Currently, all four probes may be used to identify the indicated mycobacteria grown in pure culture. A new technology for identification of both the genus Mycobacterium and of the M. tuberculosis complex directly in sputum is under study and shows promise. These probe identifications commonly are completed within 2 to 8 h, depending on the number of samples tested. The possibility of precise identification of M. tuberculosis directly in sputum within a few hours is revolutionary. ***(Wilson SM, et al, 1997 and Eltringham I J., 1999)***

IMMUNOASSAY OF MYCOBACTERIAL ANTIGENS

Antigens have been detected in liquid mycobacterial cultures only shortly after radiometric growth indices become positive. Both enzyme-linked immunosorbent assays (ELISA) and radioimmunoassays (RIA) have been used. Although still in the developmental phase, these assays appear to offer rapid species-specific identification. Monoclonal antibodies may be useful to confer specificity for individual epitomes in these assays. Dot blot immunoassays are capable of recognizing species-specific catalases. **(Raja et al , 1988)**

Direct antigen detection by immunoassay has been successfully accomplished by several laboratories in cerebrospinal fluid, and this approach may prove to be useful for the diagnosis of tuberculous meningitis. Immunoassay of mycobacterial antigen in sputum or in other clinical specimens has been found to be technically difficult, and there are only a few reports of success with this approach. **(Raja et al , 1988)**

Mycobacteriophage Typing

An old tool brought into more active use, phage typing has been useful in detecting laboratory cross-contamination, investigating epidemics of tuberculosis, and determining whether relapse cases were due to reinfection or reactivation. **(Manowska W, 1988)**

Chemical Detection of Biologic Compounds

Several new techniques have been developed to detect specific components produced either by the mycobacterial cells or by the diseased host in response to mycobacterial infection.

Rapid confirmation of tuberculous meningitis has always been difficult for the microbiologist. Recently, adenosine deaminase, a host enzyme produced by activated T cells and easily detected by a colorimetric procedure, was shown to increase in concentration during the active stages of tuberculous meningitis and to decrease to normal levels after effective antituberculosis therapy. **(Schutte CM, 2001)**

A more complicated technology detects the presence of tuberculostatic acid in the spinal fluid or serum of patients. The presence

of this compound in patients with meningitis supports a tuberculous etiology. Both of these techniques will require critical evaluation with regard to sensitivity, specificity, speed and ease of performance, and cost.

Another valuable tool has been the use of high performance liquid chromatography (HPLC) to detect the species-specific mycolic acids produced by those genera that contain these unique fatty acids. For the genus Mycobacterium, each of the species examined to date has its own unique mycolic acid pattern. When used on primary culture isolates, this technique enables species to be identified within 6 to 18 h rather than the 2 to 6 wk commonly needed for biochemical differentiation. Pilot studies on sputum samples have also revealed that strongly smear-positive specimens contain enough bacilli (> 10/ml) to enable their direct specific identification by HPLC of sputum. In addition, capillary gas chromatography has been used to study the short-chain fatty acids and cleavage products of mycolic acids from mycobacteria. Combination of this with HPLC may provide a useful method of speciating the mycobacteria. **(Schutte CM, 2001)**

Molecular detection of rifampin resistance:-

A variety of diagnostics have capitalized on the recent elucidation of molecular mechanisms of drug resistance, especially to rifampin, which in most setting is a good marker for MDR and which is almost always caused by limited number of mutates in a single gene, rpo B32 more than a dozen techniques have been described to detect relevant rpo B mutations, from simple electrophoretic techniques. ***(Cooksey R C, et al, 1998).***

The line probe assay, a straight forward amplification and reverse hybridization technique, has been available as a commercial assay for several years; good correlation with standard drug susceptibility testing in isolates from a variety of countries suggests that it could have wide applicability, though it is too expensive for most.

The line probe assay is usually used on culture isolated, but has been used on direct patients specimens in a small number of studies

F-SEROLOGICAL DIAGNOSIS OF TUBERCULOSIS

Serodiagnosis of tuberculosis has been under investigation for some years, although there is no evidence that serological diagnosis provides any more diagnostic information than can be made available from conventional microbiological investigation. Serodiagnosis using enzyme- linked immunosorbent assay does not add to diagnosis in cases where sputum smears are available and results so far in patients with negative sputum smears have been disappointing. ***(Chan S.L.; et al; 1990)***

Serological methods for diagnosis of pulmonary tuberculosis in Egypt:

Simple latex agglutination test and indirect immunoflourecent test giving sensitivity of 91.2% and 90.12% respectively and fairly good specificity (85%) by ***Ahmed 1991 and El Nashar 1983***.

ELISA in serodiagnosis of TB was used by authors to detect specific IgG antibody to purified protein derivative PPD. ***(Sobhy et al 1992, El Dafrawy et al 1994)***. It gave a sensitivity of 84%-85.7% and specificity between 90 –100% in pulmonary TB while the work of last

authors in extra pulmonary TB the sensitivity was 80% and specificity 86%.

ELISA using 38Kda recombinant antigen was utilized by ***(El Shair et al 1995)*** in diagnosis of pulmonary and extra pulmonary TB with good diagnostic value in the latter (81.2%). ***El Fiky et al, 1996*** investigated the reliability of ELISA in serodiagnosis of TB and concluded that in high clinical suspicion of TB, ELISA may be of diagnostic value, but with low clinical suspicion the results should be evaluated cautiously and bacteriological confirmation is needed.

G-Pulmonary Physiologic Changes

There are no specific changes in pulmonary function related to tuberculosis. With extensive parenchymal involvement, the vital capacity and other lung volumes are decreased. The radiographic changes appear to correlate somewhat better with a decrease in the single-breath carbon monoxide diffusing capacity. Reductions in vital capacity and total lung capacity also may result from extensive pleural involvement. Quite often there is a remarkable preservation of arterial oxygen tension, despite extensive lung destruction, which indicates a decrease in perfusion to match the decreased ventilation to destroyed areas of the lung. With extensive fibrotic residual tuberculosis, corpulmonale may supervene. Rarely, acute tuberculosis can cause diffuse infiltration of the lungs with resultant respiratory failure in a pattern resembling the adult respiratory distress syndrome. ***(Crofton and Douglas, 2000),***

TESTS TO DETECT LATENT INFECTION

Tuberculin skin testing is the standard method for detecting-latent infection with M. tuberculosis. Unfortunately, PPD shares a large number of antigens both with BCG and with environmental mycobacteria and hypersensitivity responses are relatively non specific.

TUBERCULIN SKIN TEST

In 1890, ***Robert Koch*** announced that he had discovered a cure for tuberculosis. He treats TB patients with subcutaneous doses of what he called tuberculin, a brownish transparent liquid obtained form culture filtrates of Mycobacterium tuberculosis ***(Edwards and Edwards, 1960***).

Types of tuberculin: -

1- Heat - concentrated synthetic medium tuberculin (old tuberculin) (OT): This type of tuberculin is commonly used in veterinary medicine and as antigen in multiple puncture screening tests. The international unit

(IU) of OT is defined as the logic activity contained in 0.01111 ul of the international standard; each milliliter of the standard contains 90,000 IU ***(Landi, 1984).***

2 - Purified Protein Derivative of Tuberculin (PPD): In 1934, ***Siebert and Munday*** isolated a low - molecular weight protein by precipitating culture filtrates of tubercle bacilli with trichloroacetic acid (TCA). Efforts to produce a more purified product through ammonium-sulfate (AS) precipitation resulted in PPD ***(Edwards and Edwards 1960)***. The standard for all PPD preparation is tuberculin PPD, Lot number 49608 (PPD.S) ***(American Thoracic Society, 1969).***

The IU for PPD is defined as the biologic activity contained in 0.000028 mg of PPD-S, consisting of 0.00002-mg PPD plus 0.000008 mg salts. The standard is distributed as a lyophilized powder; each ampoule contains 500,000 IU. In the US and Canada, the potency of PPD preparation is expressed in US units, or TU rather than IU ***(Landi, 1984)***. One TU is defined as 0.00002 mg of PPD-S ***(Roitt et al., 1985).***

Immune Response to Tuberculin:

The injection of tuberculin into the skin stimulates the lymphocytes and activates the cascade that lead to delayed type hypersensitivity (DTH) response. This response is called delayed because the reaction requires 24-48 hours to appear. Dermal reactivity involves vasodilatation, edema and the infiltration of lymphocytes, basophils, monocytes and neutrophils into the site of antigen injection. Antigen-specific T. lymphocytes proliferate and release lymphokines, which mediate the accumulation of

other cells at the site. Maximal responses generally occur at 72 hr. after antigen injection ***(Waksman, 1971).***

Sensitivity, specificity and positive predictive value of tuberculin skin test.

Although the tuberculin skin test is now the only method of detecting M. tuberculosis infection, the test is neither 100% sensitive nor 100% specific. Specificity is a test's ability to correctly identify persons who do not have a condition. In population with a high prevalence with (BCG), the specificity of tuberculin test will be low. ***(Bloch, 1998).***

The positive predictive value of tuberculin test is also variable. It reflects the ability of positive test to identify persons who have a condition. As the prevalence of TB infection in the population decreases, the positive predictive value of tuberculin test also decreases ***(Bloch, 1998).***

Interpretation of the Tuberculin Test:

According to the ***American Lung Association (1974)*** the following interpretation of tuberculin test is recommended:

- 10 mm or more of induration → positive reaction.
- 5 - 9 mm of induration →doubtful reaction.

Some may be specific but most likely cross reaction with number of mycobacteria other than M. tuberculosis.

Recommended Criteria for tuberculin positivity by risk group:

5mm	10mm	15mm
-HIV infected persons. -Injecting drug user (IDUS) of unknown HIV status. Recent exposure to TB -Persons with chest radiographs that suggest old healed TB	-Foreign –born persons from high prevalence countries. -Low income populations -IDUs know to be HIV seronegative. -Correctional institution/nursing home residents -Mycobacterial laboratory employees	No risk factor

(Centers for Disease Control, 1996).

False positive reaction to tuberculin:-

Infection with non-tuberculous mycobacteria: Distinguishing reactions resulting from infection with M. tuberculosis from those occurring after infection with other mycobacteria is not possible.

In general, the larger the induration size, the greater the likelihood that the reaction represents true infection with M. tuberculosis ***(American thoracic society, 1990)***

BCG vaccination: After BCG vaccination, it is not possible to distinguish between a tuberculin skin test reaction caused by virulent mycobacterial infection or by vaccination itself. ***(American thoracic society, 1990)***

False negative Reactions to Tuberculin:

(American Thoracic Society, 1981).

Potential causes of false-negative tuberculin skin test reaction.

1- Factors related to the person being tested:

- Infection:-
  - Viral (HIV, measles, chicken pox).

- Bacterial (typhoid fever, brucellosis, typhus, leprosy pertussis, overwhelming TB).
- Live virus vaccinations (measles, mumps, polio).

- Metabolic derangements (chronic renal failure).
- Nutritional factors (severe protein depletion).
- Disease affecting lymphoid organs (Hodgkin's disease, lymphoma, sarcoidosis)
- Age (new born, elderly patients whose sensitivity has waned).
- Recent or overwhelming infection with M. tuberculosis.
- Stress (surgery, burns, mental illness, and graft, versus - host reactions).

2 - Factors related to the tuberculin used:

- Improper storage (exposure to light and heat).
- Improper dilutions.
- Chemical denaturation.
- Contamination.
- Adsorption (partially controlled by adding Tween 80).

3 - Factors related to the method of administration:

- Injection of too little antigen. ,
- Delayed administration after drawing into syringe.
- Injection too deep

4 - Factors related to reading the test and recording results:

- Inexperienced reading.
- Conscious or unconscious bias.
- Error in reading

ASSESSMENT OF ACTIVITY

Abnormal chest radiographic opacities due to pulmonary tuberculosis are very common, especially in older people in developed countries and at all ages in developing countries. It is often difficult decide whether a particular lesion should be treated or whether it merits further follow up to assess activity. The following may give some guidance:

Bacteriologically positive sputum indicates activity and is an absolute indication for treatment.

- The presence of symptoms such as cough, haemoptysis, tiredness or loss of weight is suggestive that lesion demonstrated radiologically is active.
- The presence of crepitaions on auscultation, especially if persistent, is in favour of activity.

- Certain radiological appearances suggest activity:
- A cavity (unless has been previous effective treatment).
- Soft shadow, especially if wide spread.
- Shadows that extend on serial chest films. ***(Crofton and Douglas, 2000)***

Unless the lesion has calcified there is a risk of reactivation of pulmonary tuberculosis, although the risk varies with age and the type of lesion. ***(Scottish Thoracic Society, 1963)***

DIFFERENTIAL DIAGNOSIS OF PULMONARY TUBERCULOSIS

(Crofton and Douglas, 2000)

The most important conditions from which tuberculosis has to be distinguished are pneumonia, carcinoma of the bronchus, lung abscess and pulmonary infarct. In certain regions of America coccidiodomycosis, and histoplasmosis in both America and parts of Africa, have to be considered.

Pneumonia

A segmental pneumonia with soft upper zone opacities may mimic pulmonary tuberculosis. In contrast to tuberculosis, where symptoms may be absent or prolonged, the acute pneumonic patient usually has symptoms of fairly recent onset. A history of contact with tuberculosis may suggest this diagnosis in young people. The diagnosis of

tuberculosis is made by sputum examination and tuberculin testing. If the patient is symptomatic, an oral antibiotic should be prescribed and if the radiographic opacities have not cleared or improved in 2-3 weeks then tuberculosis is more likely.

Carcinoma of the bronchus

This differential diagnosis arises in the middle aged and elderly age groups. Consolidation distal to a proximal carcinoma, particularly in the upper zone, may be cavitated and closely mimic tuberculosis. Occasionally, primary tuberculosis in the elderly presents with a peripheral lesion and enlarged hilar nodes, closely mimicking carcinoma. Sputum examination for malignant cells and acid fast bacilli may differentiate the two but, bonchoscopy may be required to make the diagnosis.

Lung abscess

Lung abscess due to staphylococcus pyogenes or klebsiella pneumoniae is usually an acute sever illness with marked leucocytosis and the organism readily isolated from blood and sputum. With cavitary tuberculosis the sputum is usually, but not always, positive on direct smear.

Pulmonary infarction

Upper zone pulmonary infarct, especially if bilateral and/or cavitating may give rise to diagnostic difficulty. Routine examination, evidence of deep vein thrombosis and serial chest films that show rapid change in pulmonary infarction usually distinguish the two conditions.

COMPLICATIONS (*Crofton and Douglas, 2000)*

Pleurisy

Pleurisy occurs commonly in pulmonary tuberculosis. A classical pleural rub may be heard.

Tuberculous empyema

Tuberculous empyema was commonly found following artificial peumothorax therapy. It still present as many as 30 years after initial infection. The diagnosis is made by the demonstration of acid fast bacilli on direct smear in pus from the pleural space. Chemotherapy and tube suction may resolve the situation but further surgical procedures such as decortications may be indicated. ***(Neihart RE. And Hof DG; 1985).***

Tuberculous laryngitis

These are seen in patients with positive sputum and relatively sever disease. It causes hoarseness progressing to pain on swallowing. Laryngoscopic examination and biopsy are important in establishing the diagnosis.

Tuberculosis of other organs

Tuberculosis may not be confined to the lung. In the male the testis should be examined routinely, and routine urine examination for tubercle bacilli is advisable.

Chronic obstructive airway disease

There is no doubt that a clinical pattern of disease almost indistinguishable from that of chronic bronchitis and emphysema with severe airways obstruction may result in patients with sever fibrotic

pulmonary disease following tuberculosis***.(Snider GL.,et al;1971 & Willcox PA and Ferguson AD.;1989).***

Cor pulmonale

Cor pulmonale develops secondary to extensive fibrotic disease, with distortion of pulmonary parenchyma, emphysema and airways obstruction.

Amyloidosis

This complication is now rare but may still be seen in association with tuberculous empyema. Diagnosis may be made by the staining of rectal mucosa, liver or kidney biopsy.

Aspergilloma

Infection of tuberculous cavities by aspergillus fumigatus is recognized. Surgical resection of lesions causing major problems (i.e. massive haemoptysis) may be advisible. ***(Al-Majed SA.et al; 1990).***

Carcinoma of the bronchus

More common in patients with inactive tuberculous disease. Both are common in cigarette smokers and may occur together. The concept of `scar carcinoma` although attractive, has never been fully established. ***(Steinitz R.; 1995).***

Adult respiratory distress syndrome

The adult respiratory distress syndrome may complicate post primary tuberculosis***.(Dyer RA. And Potgieter PD.; 1984).***

Pulmonary tuberculoma

Tuberculoma presents occasionally as an incidentally discovered solitary pulmonary nodule. The principal differential diagnosis is from bronchogenic carcinoma. ***(Ishada T. et al; 1992).***

Poncet`s disease

Poncet`s tuberculous polyarthritis first described in 1897,reiterated as recently as 1984,this polyarthritis resembling rheumatic fever, may occur in association with post primary pulmonary tuberculosis. It resolves with treatment. (***Wilkinson AG.and Roy S.; 1984).***

AIM OF WORK

The aim of this study is to assess the role of adenosine deaminase enzyme (ADA) level in serum and broncho alveolar lavage fluid (BALF) in the diagnosis of pulmonary tuberculosis and to differentiate it from other lung diseases.

MANEGMENT OF PULMONARY TUBERCULOSIS

NOTIFICATION:

All cases must be notified as this is a statutory requirement ***(Ormerod et al., 1996).*** and initiates contact tracing if appropriate.

HOSPITALIZATION:

Hospitalization for initial therapy of tuberculosis is not necessary in most patients, though it should be considered if a patient is incapable of self cares or is likely to expose susceptible individuals to the risk of tuberculosis.

A private room with appropriate ventilation and instruction of the importance of covering the mouth while coughing are sufficient infection control measures for hospitalized patient receiving effective chemotherapy ***(Tiernery et al., 1995)***. Monthly follow up of compliant out patient is recommended including sputum smear and culture till conversion occurs ***(Kasik, 1994).***

DRUGS IN CURRENT USE:

ISONIAZID

Isoniazid is the most widely used of the antituberculous agents. In many respects it is an ideal agent, bactericidal, relatively non-toxic, easily administered and inexpensive. It is highly active against M. Tuberculosis (most strains begin inhibited in vitro by concentrations of 0.05 to 0.20

μg/mL). Absorption from the gastrointestinal tract is nearly complete, with peak blood concentration occurring 1 to 2 hours after administration.

A usual dose of 3 to 5 mg / kg body weight produces a peak concentration of approximately 5 μg /mL. The drug penetrates well into all body fluids and cavities producing concentrations similar to those found in serum ***(Kumar D, et al; 1993).***

Hepatitis is the major toxic effect of isoniazid .Alcohol consumption was also identified as a risk cofactor ***(Kopanoff et al, 1998)*** Peripheral neuropathy, most likely caused by interference with metabolism of pyridoxine is associated with isoniazid administration, but is uncommon at a dose of 5 mg / Kg. In persons with conditions in which neuropathy is common (diabetes, uremia, alcoholism, malnutrition), pyridoxine should be given with isoniazid. It is also advisable to give pyridoxine with isoniazid to women who are pregnant and to persons who have a seizure disorder. Mild central nervous system effects are common with isoniazid. The interaction of isoniazid and phenytoin increases the serum concentration of both drugs. When these drugs are given concomitantly, the serum level of phenytoin should be monitored and the phenytoin dosage decreased if necessary ***(American Thoracic Society, 1994).***

Rifampin:

Rifampin is bactericidal for M. tuberculosis. The drug is relatively nontoxic and is easily administered. It is quickly absorbed from the gastrointestinal tract, with peak serum concentration (of 6 to 7 ug/ml) occurring 1.5 to 2 hours after ingestion. Most strains of M. tuberculosis are inhibited in vitro by concentrations of 0.5 μg /ml.

Although approximately 75% of the drug is protein bound, it penetrates well into tissues and cells. Penetration through non-inflamed meninges is poor, but therapeutic concentrations are achieved in CSF when the meninges are inflamed, the most common adverse reaction to rifampin is gastrointestinal upset. Other reactions include skin eruptions, hepatitis and rarely thrombocytopenia and cholestatic jaundice. In general, the frequency of these reactions is quite low ***(Bass. et al., 1995).***

Because rifampin induces hepatic microsomal enzymes, it may accelerate clearance of drugs metabolized by the liver. This include methadone; coumarin derivatives, gluocorticoids, estrogens, oral hypoglycemic agents, digitoxin, anti-arrhythmic agents (quinidin, verapamil, mexiletine), theophylline, anticonvulsants, ketoconazole and cyclosporin ***(Baciewicz, 1987).***

By accelerating estrogen metabolism, rifampin may interfere with the effectiveness of oral contraceptives. Current literature should be consulted concerning the possible drug interactions ***(Rizach and Hillman, 1985).***

In adults, intermittent administration of doses of rifampin larger than 10 mg/ kg may be associated with thrombocytopenia, influenza - like syndrome, hemolytic anemia and acute renal failure. These reactions are uncommon at the recommended dose of 10 mg/kg. Rifampin is excreted in urine, tears, sweat and other body fluids and it colors them orange. Patients should be advised of discoloration of body fluids and of possible permanent discoloration of soft contact lenses ***(Medical Section, 1994).***

Pyrazinamide: -

Pyrazinamide is bactericidal for M. Tuberculosis in an acid environment. The drug is against organisms in macrophages, presumably because of the acid environment within the cell.

Absorption from the gastrointestinal tract is nearly complete, with peak serum concentrations occurring approximately 2 hours after ingestion. Serum concentrations generally range from 30 to 50 μg /ml with doses of 20 to 25 mg/kg. Pyrazinamide penetrates well into most tissues, including the CSF at a pH of 5.5 the minimal inhibitory concentration of Pyrazinamide for M. tuberculosis is 20 μg /ml ***(American Thoracic Society 1994).***

The most important adverse reaction to Pyrazinamide is liver injury. This dose not appear to be significant increase in hepatotoxicity when Pyrazinamide in a dose of 15 to 30 mg/kg is added to a regimen of isoniazid and rifampin during the initial 2 months of therapy ***(Steele and Desprez, 1988).***

Hyperuricemia occurs frequently, occasionally accompanied by arthralgia, but acute gout is uncommon. Treatment with salicylates generally provides symptomatic relief of Pyrazinamide-related arthralgia. Skin rash and gastrointestinal intolerance are also seen ***(Medical Section 1994).***

Ethambutol:

Ethambutol in usual doses is generally considered to have bacteriostatic effect on M. tuberculosis. It may have a bactericidal effect when given in the higher dosage used for intermittent therapy. The drug is easily administered and has a low frequency of adverse reaction. Peak plasma concentrations occur 2 to 4 hours after ingestion. With doses of 15 mg/kg the peak concentration is approximately 4 μg /ml. In persons with normal renal functions, serum half-life is approximately 4 hours.

The half life is prolonged and the drug accumulates in persons with renal insufficiency. Most strains of M. Tuberculosis are inhibited in Vitro by concentrations of the drug in a range from 1 to 5 ug/ml. Cerebrospinal fluid concentrations of Ethambutol are low even in the presence of meningeal inflammation, averaging 1 to 2 ug/ml after a dose of 25 mg/kg. Retrobulbar neuritis is the most frequent and serious adverse effect of Ethambutol. Symptoms include blurred vision, central scotomata and red-green color blindness ***(Grange, 1997).***

This complication is dose related, occurring in less than 1% of persons given a daily dose of 15 mg/kg and increasing with a daily dose of 25 mg/kg. The frequency of ocular effects is increased in patients with renal failure, presumably because of increased serum concentration of the drug. Visual symptoms commonly precede a measurable decreased visual acuity.

Patients should be informed to report any change in vision. In children who are too young for assessment of visual acuity and red-green color discrimination, Ethambutol should be used with particular caution; consideration should be given to the use of possible alternative drugs ***(Bass. et al., 1995).***

Streptomycin: -

Streptomycin is bactericidal in an alkaline environment. Because the drug is not absorbed from the gut, it must be given parentrally. Peak serum concentration occurs approximately 1 hour after an intramuscular dose. With a dose of 15 mg/kg, the peak concentration is in the range of 40 ug/ml, most strains of M. tuberculosis are inhibited in vitro at a concentration of 8 ug/ml. The half-life in blood is approximately 5 hours. Excretion is almost entirely renal. The drug should be used in reduced dosage and with extreme caution in patients with renal insufficiency ***(American ThoracicSociety, 1994).***

The drug has good tissue penetration; however, it enters the cerebrospinal fluid only in the presence of meningeal inflammation. The most common serious adverse effect of streptomycin is ototoxicity. This usually results in vertigo, but hearing loss may also occur.

Ototoxicity is more likely if other ototoxic drugs are given concomitantly. Streptomycin has less adverse effect on the kidneys than kanamycin and capreomycin, but nephrotoxicity occasionally occurs. Renal toxicity may be increased in patients with pre-existing renal insufficiency or with simultaneous use of other nephrotoxic drugs. The risks of ototoxicity and nephrotoxicity are related both to cumulative dose and to peak serum concentrations. A total cumulative dose of more than 120g should not be given unless other therapeutic options are not

available. Both ototoxicity and nephrotoxicity are more common in persons older than 60 years of age.

Streptomycin should be avoided, or used in reduced dosage, if possible, in its age group ***(American Thoracic Society 1994).***

Para Amino salicylic Acid:

PASA is a bacteriostatic anti-tuberculous drug. The usual therapeutic dose is approximately 150 mg/kg by mouth, or into a maximal dosage of 10 to12 g/d. the high doses are necessary because Para - amino salicylic acid is rapidly execrated. The delayed release granules should be given with acidic food or drink, such as orange juice. This dose represents a significant sodium load when the tablet preparation is used. The adverse reactions to the drug include a high frequency of gastrointestinal upset (nausea, vomiting and diarrhea), hypersensitivity reaction in 5 to 10 % of patients, and rarely hepatitis ***(American Thoracic Society 1994).***

Ethionamide:

Ethionamide is a bacteriostatic derivative of isonicotinic acid. It is available in 250 mg tablets. The usual daily dose is 15 to 20 mg/kg, with a maximum daily dose of 1 g. Nausea, vomiting, loss of appetite and abdominal pain are the most common adverse effects of ethionamide. In many patients it is necessary to increase the dose to the full amount gradually. Administering ethionamide at bed time with anti-emetic drug taken 30 min. before the dose, and occasionally, a hypnotic is often useful to maintain treatment. Ethionamide may also cause hepatitis although the frequency is probably no greater than with pyrazinamid. Hepatic enzymes

(Aspartate amino-transferase, alanine aminotransferase) should be monitored monthly, and the drug should be discontinued if there is a five fold elevation in enzymes even in the absence of symptoms. Other adverse effects that occur with ethionamide include artheralgia, impotence, gynecomastia, photosensitive dermatitis, hypothyroidism and a metallic taste in the mouth ***(American Thoracic Society, 1994).***

Cycloserine:

Like ethionamide, cycloserine is a bacteriostatic anti-tuberculous agent that is useful in certain limited situations. It is available in 250 mg capsules and the usual dose is 15 to 20 mg/kg, with a maximal dosage of 1g/d. The major adverse reactions are emotional and behavioral disturbances including psychosis. Patients who have a history of psychological problems (for example, depression) or who have a chronic psychiatric condition are more likely to experience the central nervous system effects of cycloserine. Regular assessment of the mental status of these patients is recommended in monitoring for these adverse effects. Convulsions and peripheral neuropathy also occur, especially when the drug is used with isoniazid. For this reason 150 mg/d of pyridoxine should be given with cycloserine. Cycloserine interferes with the elimination of phenytoin, especially when taken with isoniazid; generally, the dosage of phenytoin must be reduced ***(American Thoracic Society, 1994).***

Capreomycin:-

Capreomycin is an injectable anti-tuberculous agent. It is available in 1g vials, and the daily dosage is 15 to 30 mg/kg by intramuscular injection, or 1 g as the maximal dosage. Capreomycin is toxic to the eighth cranial nerve, causing high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs. An audiogram performed at base line and again at least every other month while the patient is receiving therapy is recommended in addition to periodic examinations for vestibular function. Renal toxicity is somewhat more common with capreomycin than with streptomycin, and it may be associated with electrolyte disturbances secondary to tubular damage, as well as an elevated creatinine level. Older patients are generally more susceptible to the toxic effects of capreomycin and the maximal daily dosage should be limited to 750 mg ***(American Thoracic Society, 1994).***

Kanamycin:

Kanamycin is also an injectable agent. It is available in 75mg, 500 mg and 1g vials. The usual daily dosage is 15 to 30 mg/kg given intramuscularly, with a maximal daily dosage of 1g. Auditory toxicity is more common with kanamycin than with streptomycin and capreomycin. Monthly audiometery is recommended while patients are being treated with this drug. Vestibular toxicity is rare. Renal toxicity occurs at a frequency similar to that of capreomycin and regular monitoring of serum creatinine is recommended **(American Thoracic Society, 1994).**

Thiacetazone:

Thiacetazone is used in many developing countries because it is inexpensive. Although thiacetazone is biochemically related to isoniazid, it is bacteriostatic and more toxic than isoniazid. The usual adult dosage is 150 mg/day by month. Commonly, it is combined in a single tablet containing 300 to 400 mg of isoniazid and 150mg of thiacetazone ***(American Thorocic Society, 1994).***

Gastrointestinal upset occurs in as many as 10% of patients taking the drug, and it includes nausea and vomiting. Less frequent adverse effects include jaundice (< 1%), reversible bone narrow suppression (0.2%) and rashes (3.9%). Cutaneous reactions from thiacetazone may be severe and if the drug is not stopped, an exfoliative dermatitis or Stevens Johnson syndrome may occur. These reactions are especially frequent in HIV infected persons, and the drug is contraindicated in this population. Thiacetazone may also potentiate the vestibular toxicity of streptomycin. Geographic variation in adverse effects has been observed with patients in East Africa tolerating the drug better than Asians ***(American Thoracic Society 1994).***

Amikacin: -

Amikacin is highly bactericidal against the M. Tuberculosis in vitro. It is given as a single dose of 15 mg/kg by intramuscular injection five times weekly. The solution for intravenous use is prepared by adding the content of a 0.5 g vial to 100 ml sterile diluent (i.e. normal saline, 5% dextrose in water). The total intravenous single daily dose is also 15mg/kg given over 30 min. average peak serum concentration (C max) is 21 ug/ml 1 hour after intramuscular administration of 7.5mg / kg single dose ***(peloquin, 1991).***

The minimal inhibitory concentration (MIC) for amikacin is approximately 4 to 8 ug/ml for a wide range of strains of M. tuberculosis ***(Heifets, 1991).***

The major side effect of amikacin is nephrotoxicity. The dose or administration frequency of amikacin should be adjusted if renal insufficiency emerges. Blood urea, nitrogen and creatinine levels should be monitored weekly or biweekly and if elevated, warrant a creatinine clearance study. Other side effects include vestibular dysfunction, hearing loss, chemical imbalance (decreases in calcium, potassium and magnesium levels should be monitored weekly or biweekly), circumoral numbness and minor dizziness. A baseline audiogram should be done prior to treatment and monthly thereafter if the patient is receiving one injectable drug, twice monthly if receiving two. When there is similar susceptibility to capreomycin and amikacin, capreomycin should be used if the patient is 60 years of age or older since older patients seem to experience more renal and eight - nerve toxicity with amikacin than with capreomycin, ***(Isman and Madsen, 1989).***

QUINOLONES

A number of fluoroquinolones have been developed that show in vitro activity against M. Tuberculosis. The target of the quinolones is a DNA gyrase. Ofloxacin and ciprofloxacin are compounds in this family ***(American Thoracic Society, 1994).***

In general quinolones are well tolerated. Gastrointestinal symptom dizziness and hypersensitivity are the most commonly reported adverse effects. Changes in laboratory parameters that may be associates

with adverse effects include elevation of aspartate aminotransferase, alanine aminotransferase, eosinophilia, leukopenia and elevated serum creatinine. The quinolones are primarily cleared by renal excretion and the dosage should be adjusted for those with creatinine clearance of < 50 ml/min. It was found that toxicity is more dependent on dose than on the duration of therapy ***(*KiaNoury D, et all, 2000*).***

Doses of 750mg ciprofloxacin and 400 mg ofloxacin twice a day are recommended by the manufacturers for the treatment of severe respiratory tract infection. The data on the use of these agents for treatment of tuberculosis is limited ***(Tsukamura et al, 1995).***

Refabutin

Refabutin is a rifampin spiropiperidyl derivative that shows activity in vitro against certain rifampin resistant strains of M. tuberculosis. The MIC for strains of M. tuberculosis that are susceptible to rifampin is low: < 0.06 ug/L. The MIC for rifampin resistant strains; are significantly higher than for the rifampin -susceptible strains (range 0.25 to 16 ug/ml), indicating cross resistance between these drugs. The wide range of MICS for these strains is an indication that the rifampin-resistant strains have varying degrees of susceptibility to rifabutin ***(American Thoracic Society, 1994***). Rifabutin is rapidly absorbed from gastrointestinal tract, with peak serum levels of 0.49 ug/ml occurring in 4 hours after administration of 300 mg ***(O'Brien et al., 1997).***

The half-life in serum is 16 hours and tissue levels are 5 to 10 fold higher than that in serum. Protein binding for rifabutin appears to be 25% of that seen for rifampin. The drug is eliminated at similar

concentration by the kidney and liver. The implication for the use of rifabutin in clinical chemotherapy is not yet clear. Strains of M. tuberculosis with MICs < 0.5 ug/ml can probably be considered as "moderately susceptible" to rifabutin (***Heifets et al., 1999).***

In studies of acute and chronic toxicity in several species of animals, rifabutin was of comparable toxicity to or less toxic than rifampin. One analysis of rifabutin toxicity in human found that the most common adverse reaction to rifabutin were hematologic and hepatotoxic reaction. The data suggest that rifabutin is probably not more hepatotoxic than rifampin. Other reactions include gastrointestinal upset and hypersensitivity ***(O'Brien et al., 1997).***

Clofazimine

Clofazimine is a substituted iminophenazine bright-red dye that exerts a slow bactericidal effect on M. leprae. Clofazimine inhibits mycobacterial growth and binds preferentially to mycobacterial DNA causing inhibition of transcription. In addition to this direct antimycobacterial property, Clofazimine in combination with gamma interferon restores the inhibition of phagocytic and microbicidal activities caused by a 25 kilo Dalton fraction from M. Tuberculosis, indicating the possible use of these two phagocyte-priming agents for the immunotherapy of tuberculosis ***(Parak and Wadec, 1991).***

Adverse reactions include discoloration of the skin, gastrointestinal upset, severe and life threatening abdominal pain and organ damage caused by clofazimine, crystal deposition and asymptomatic discoloration of the eye ***(Garrelts, 1991)***

COMBINATION OF BETA-LACTAM ANTIBIOTICS AND BETA-LACTAMASE INHIBITORS: -

Amoxicillin is a semi synthetic beta-lactam antibiotic, an analog of ampicillin, with a broad spectrum of bactericidal activity against many gram positive and gram negative microorganisms. The addition of betalactamase inhibitor to amoxicillin greatly improves its in vitro activity against M. tuberculosis. The, beta-lactam inhibitors (i.e., clavulanic acid) possess intrinsic antimycobacterial activity but they are able to inhibit the enzyme in part responsible for the resistance of M. tuberculosis the beta-lactam antibiotics. In one in vitro study, the MIC of amoxicillin plus clavulanic acid was 4 mg/ml compared with > 32 mg /ml for amoxicillin alone when tested against 27 strains of M. tuberculosis ***(Wong et al.,1988).***

After an oral dose of 500 mg of amoxicillin, peak serum concentration of 7.5 ug/ml is achieved in 2 hours. There are no in vivo studies using this drug combination against M. tuberculosis. Beta - lactam antibiotics penetrate poorly into mammalian cells, and this characteristic may limit the effectiveness of these agents in therapy for tuberculosis ***(Parentif, 1989).***

RECOMMENDED REGIMENS:

The NTP 1998 recommends the use of the following drugs in the different treatment regimens:

- Rifampicin -R

- Isoniazid -H
- Pyrazinamide -Z
- Ethambutol -E
- Streptomycin -S

In accordance with the WHO and international union against tuberculosis and lung disease (IUATLD) guidelines 1998, anti tuberculous treatment consists of an initial and a continuation phase. During the initial phase the majority of TB bacilli will be killed. In the continuation phase the remaining (dormant) TB bacilli will be eliminated.

REGIMENS RECOMMENDED BY NTP EGYPT:

TB Treatment category	***TB Patients***	***TB Treatment regimens***	
		Initial phase	***Continuation phase***
I	-New smear-positive TB -New cases of server forms of extra-pulmonary TB -New cases of severe forms of smear negative TB	2 month EHRZ or 2 month SHRZ	4 month HR or 6 month HE
II	Sputum smear positive -relapse -treatment failure -treatment after interruption	2 month (SHRZE) plus one month (HRZE)	5 month HRE
III	- New less negative PTB. -New smear severe forms of extra pulmonary TB	2 month HRZE or 2 month HRZS	4 month HR or 6 month HE

IV	chronic case (still sputum positive after full course of supervised retreatment	Not applicable; refer to specialized center where second-line drugs are available

(National tuberculosis control Programme of Egypt 2005).

BCG VACCINE

In 1908, Albert Calmette and Camille Guerin began to subculture a strain of M. tuberculosis from a cow with tuberculous mastitis. After 13 years and 230 serial subcultures the strain was no longer virulent in animals, and in 1921 the use of Bacilli Calmette-Guerin (BCG) in humans was begun. This is a live vaccine, and it is the most widely used vaccine in the world today.

Due to genetic variation of strains and differences in production techniques, not all BCG vaccines are identical. The vaccine does not protect against infection with the tubercle bacilli, and the efficacy of BCG in preventing- active disease has ranged from 20 to 80 percent in trials conducted. Explanations for this variability in vaccine efficacy may be related to regional differences in environmental mycobacteria and different strains of BCG used in the trials.

Exposure to infection with environmental mycobacteria may provide cross-protection against tuberculosis and BCG may add little to that protection ***(Fine, 1995).***

A diagnosis of M. tuberculosis infection should be considered for a BCG vaccinated person with a positive skin test if any of the following condition is met:

1) The size of the skin test induration is large.

2) There is history of contact with a person with tuberculosis.

3) There is a family history of tuberculosis.

4) The person's country of origin has a high prevalence of tuberculosis. ***(Centers for Disease Control, 1996).***

PATIENTS AND METHODS

This study was conducted on fifty patients, admitted to El-Giza chest hospital and chest department, Cairo University during period between October 2004 and March 2005.

Those patients were classified into (4) groups: -

Group (I): (20) Patients with sputum (+ve) for AFB.

Group (2): (10) Patients with bronchogenic carcinoma, diagnosed clinically, radiologically & histo-pathologically.

Group (3): (10) Patients with pneumonia, diagnosed clinically, radiologically and bacteriologically.

Group (4): (10) Normal healthy persons.

ALL persons were subjected to the following: -

(1) Thorough history taking and clinical examinations.

(2) Plain chest x-ray (postero-anterior & lateral view).

(3) Sputum for AFB.

(4) Routine lab. Including:

- CBC & Differential count.
- Liver & Renal Function Tests.

(5) ADA in serum & BAL fluid

(6) CT- Scan in selected cases.

Those patients were excluded according to these criteria:

- Patients with Diabetes Mellitus
- Immunocompromised patients
- Patients on corticosteroids
- Patients with hepatic and renal impairment

Collection of sputum specimens in TB patients

Early morning sputum sample was obtained from each patient on 3 successive days. Patients were instructed to take deep breath, hold it momentarily then cough vigorously into sterile screw-capped 50 ml plastic containers.

Passage of the Fiberoptic Bronchoscope

The shaft of bronchoscope was lubricated with lignocaine jell and was advanced into the nostril under direct vision. Gentle pressure was required and the instrument should never be forced. If the nasal approach was too narrow to permit the shaft of the bronchoscope to pass, oral route was used.

As the instrument was advanced, the tip was flexed downwards and when the glottis and larynx come into view the mobility of vocal cords was assessed and 2 ml of lignocaine were injected through FOB on the vocal cords.

Then quickly the bronchoscope was advanced through the opening but should not be forced. Once the vocal cords have been passed on additional 2ml aliquot of xylocaine instilled through the suction channel to suppress coughing ***(seaton et al.; 1989).***

Broncho alveolar lavage technique

The technique is accomplished by wedging the tip of the bronchoscope into a segmental bronchus which harbors the abnormal shadows in the x-ray (for the case) and into the middle lobe of the lingula (for the control). Other lobes can be used, but lavage of the upper lobe is more difficult because of the tight hend in the bronchoscope imposed by the anatomy of the upper lobe bronchi. ***(Abdel-Hakim et al.; 1989).***

Once the bronchoscope was wedged, 5 sequential aliquots of 20 ml 0.9% sterile saline is injected into the channel part. The fluid is immediately

pulled back with gentle suction following each aliquot. The lavage fluid was pooled in a sterile bottle.

METHODS OF ASSESSMENT OF ADENOSINE DEAMINASE (ADA)

Principle:

The equilibrium of reaction is far to the right, Ammonia is determined in the ***Chanev and Marbach*** modification of the Berthelor reaction, ammonia forms an intensely blue indophenol with sodium hypochlorite and phenol in alkaline solution. Sodium nitroprusside is the catalyst. The ammonia concentration is directly proportional to the extintion of the indophenol. The reaction catalyzed by ADA is stopped at the end in the incubation period by the addition of phenol nitroprusside solution.

ADA Inosine + NH_3 (1) adenosine + H_2O

Optimum Conditions for Measurements

The optimum conditions for measurements are 20 mM adenosine, phosphate buffer (ionic strength ca. 0.10) and a ph range between 6.2 and 6.8.

None of the other coated methods employ optimum conditions. All the ADA activities given in the literature are to a differing extent lower than the values of ***Galanti and Guisti***. According to recent results in our laboratory the optimum adenosine concentration for assay of ADA activity in serum is the same for normal subjects and for patients with various diseases According to the rate of the ADA reaction increases up to 64 ºC, but the data are not suitable for calculation of the temperature coefficient. According to the rate of the reaction at 37ºC is 2.2 times that at 25ºC.

Measurements at different temperatures may require different measuring condition (cf.p. 127). Nevertheless, results obtained under the same measuring conditions but at different temperatures were formerly compared with each other ("conversion factors" were determined). Such conversion factors may be correct if determined with a relatively large proband collective; however, they cannot be applied generally to the individual case (cf. P. 129). The value of the following relative reaction rates thus lies in being able to appraise the temperature dependence of the reaction and at the most to compare qualitatively values up to the limit of normal.

ºC	25	30	37
	1.1	1.30	1.85

Equipment

Spectrophotometer, spectrum-line photometer or simple photometer (with tungsten lamp and filter) suitable for accurate measurements at wavelength between 620 and 650 nm; water bath (37ºC)

Reagents

1- Sodium dihydrogen phosphate, NaH2PO4.H2O

2- Disodium hydrogen phosphate, Na2HPO4.12H2O

3- Adenosine crystalline, chromatographically pure.

4- Phenol. A.R.

5- Sodium nitroprusside, Na2 (Fe [CN] 5.NO) 2H2). A.R.

6- Sodium hypochlorite, NaOCL

7- Sodium hydroxide. NaoH

8- Ammonium sulphate. (NH4) 2SO4

Preparation of Solution

Prepare all solutions with doubly distilled, ammonia- free water. Ammonia can be removed by addition of a little H2SO4 and KMno4 and a second distillation from a glass apparatus. This precaution is particularly necessary if the ammonia content of the tap water is high.

1. Phosphate buffer (50 mM; pH 6.5): Dissolve 4.73g. NaH2PO4 H2o and 5.62g. Na2HPO4 12H2o in distilled water and dilute to 1000 ml. with boiled distilled water.

2. Buffered adenosine solution (21 mM adenosine, 50mM phosphate, pH 6.5): Add ca. 15 ml. phosphate buffers (1) to 140 ml. adenosine in a 25 ml. volumetric flask, warm in a hot water bath and cool under running water. Adjust to pH 6.5 and dilute to 25 ml. with phosphate buffer (1).

3. Ammonium sulphate stock solution (15 mM): Dissolve 1.982 g. anhydrous ammonium sulphate in ammonium free distilled water, make up to 1000 ml. and mix thoroughly.

4. Ammonium sulphate standard solution (75 μM; 0.15 μval, NH3/ml.): Dilute 0.5 ml. ammonium sulphate stock solution (III) (precision pipette) to 100 ml. with phosphate buffer (1).

5. Phenol nitroprusside solution (106 mM phenol; 0.17 mM sodium nitroprusside): Dissolve 10 g. phenol and 50 mg. Sodium nitroprusside in 500 ml. distilled water and dilute to 1000 ml.

6. Alkaline hypochlorite solution (11mM NaOCL; 125 nM NaOH): Mix 125 ml. 1N NaOH and 16.4 ml. Clorox (contain 5% w/v NaOCL) to 1000 ml. with distilled water.

Procedure

Collection, Treatment and Stability of Sample.

Use venous blood. Addition of oxalate (1mg/ml.). Citrate (1 mg./ml.) or EDTA (1 mg./ml.), doses not interfere with the assay. According to

heparinized plasma can also be used, but we found that addition of liquemin (4µl. /ml.) Cause slight inhibition of ADA, presumably because of the phenol content of the anticoagulant. Addition of fluoride gives unsatisfactory results. Use only serum or plasma free from heamolysis, because human erythrocytes have a high ADA content. The samples should not be stored for longer than 48 – 72 hr. at 4˚c.

Stability of enzyme in sample:

The information of the relatively high stability of ADA in serum varies: at least 1 day at room temperature without loss of activity; up to 1 month at 4˚c with slight loss of the activity. Storage of sera for more than 5 – 6 days at 4˚c result in liberation of ammonia, even if bacterial contamination is avoided. This gives high blank values.

Assay system:

Wavelength: 620 – 650 nm; light path: 1 cm; incubation volume: 1.05 Ml. incubation temperatures: 37˚c; final volume: 7.05 ml. Read against water. Also prepare a sample blank and a reagent blank.

Pipette successively in test tube:	Reagent blank	Standard	Sample blank	Sample
- Phosphate buffer (I) Buffered adenosine solutio (II) -Ammonium phosphate standard solution (IV) - Sample (serum) - Distilled water	1.0 ml. - - 0.05 ml	- - 1.0 ml. 0.05 ml	- 1.0 ml. - - -	- 1.0 ml. 0.05 ml -

The addition of distilled water can be omitted without causing any appreciable error. Mix and stopper tube with parafilm. Incubated for 60 min. in a 37˚c water bath.

phenol nitroprusside solution (V)	3.0 ml	3.0 ml	3.0 ml	3.0 ml
- Sample (serum)	-	-	0.05 ml	-
Alkaline hypochlorite solution (VI)	3.0 ml	3.0 ml	3.0 ml	3.0 ml

Add solution V and VI in the given in the given order and mix the content 0f the tube before pipetting into the next tube.

Incubate for 30 min. in a 37˚c water bath. Measure extinctions against distilled water.

If any extinction value exceeds 1.000 dilute the sample 2 – 5 times with distilled water and measure again. With this value as a guide dilute serum accordingly with phosphate buffer (I) and repeat the assay.

Calculations

Volume activity = (E sample _ E sample blank)/ (E sample _ E sample blank) x 50 [U/L]; 37˚c

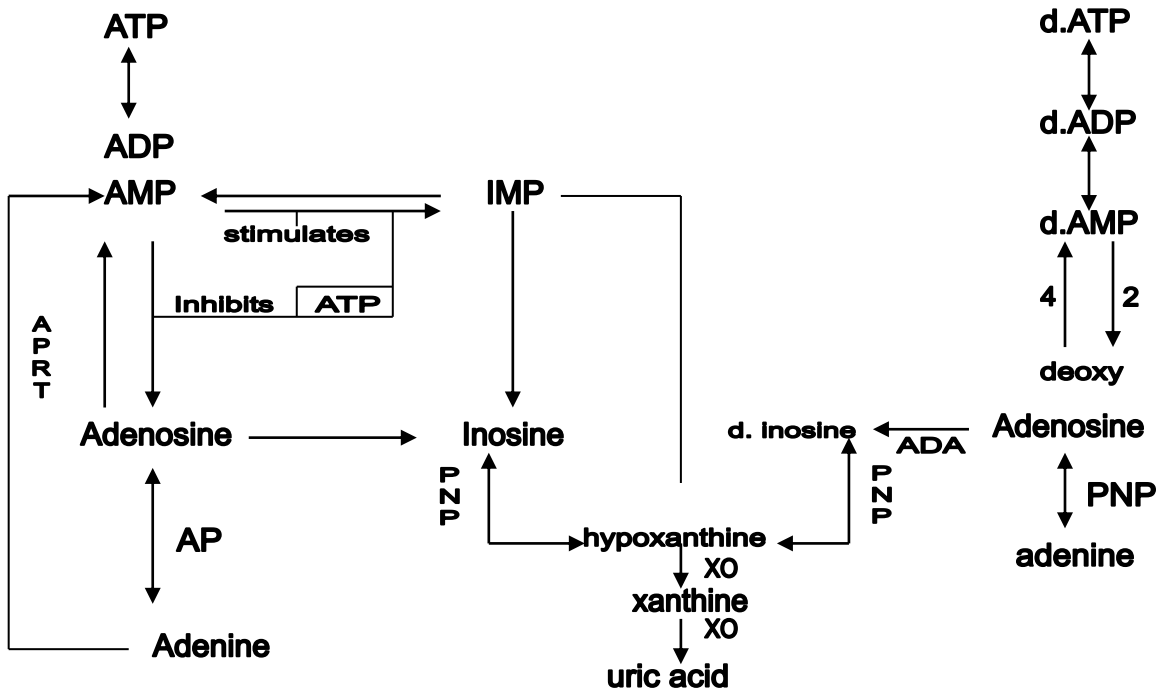
ADENOSINE DEAMINASE (ADA)

Adenosine deaminase (ADA), Adenosine aminohydrase, I.U.B.: 3.5.4.4) is a purine catabolic enzyme ubiquitous in mammalian tissue. In vitro it catalyzes deamination of both adenosine and 2'- deoxyadenosine to inosine and 2'- deoxyinosine respectively.

Adenosine + H2O ⟶ Inosine + NH3

(Hershfield, M, et al, 1987)

CATABOLIC PATHWAYS INVOLVING ADA (Hershfield, M, et al, 1987)



1 = Adenylate deaminase 2 = 5'- nucleotidase.

3 = Adenosine kinase 4 = Deoxycytidine kinase.

ADA = Adenosine deaminase AP= Adenosine phosphorylase

PNP = Purine Nuclioside Phosphorylase

HGPRT = Hypoxanthine –Guanine Phosphoribosyl Transferase.

APRT = Adenine Phosphoribosyl Transferase

Distribution:

On estimation of ADA activity in human tissues***,(Adams and Harkness, 1976)*** found that the thymus during childhood contain very much higher ADA levels than in any of the other tissues studied . Intermediate activities were obtained from spleen, lymph nodes, skin, cerebral cortex, liver and kidney had relatively low levels. ADA level is ten times higher in lymphocytes than in erythrocytes ***(Gajdos, 1978)*** and ten folds higher in T- lymphocytes than in B lymphocytes and varies during differentiation of T- lymphocytes with increased activity in the immature or undifferentiated stages (***Barton et al, 1979. Shore et al 1981).***

The enzyme activity decreases substantially during mitogenic ***(Hovi, et al, 1976)*** and antigenic ***(Hall, 1963)*** responses of lymphocytes and conversely, lymphocytes blastogenesis is inhibited by inhibitors of adenosine deaminase ***(Carson and Seegmiller , 1976)***

PROPERTIES

ADA biochemical properties have been studied in different species using conversional portion staining and electrophoretic techniques, purified ADA from calf intestine and calf serum have been shown to exist in multiple molecular forms ***(Cory et al, 1967).***

Similar isoenzymes patterns were observed in crude tissue extracts by ***Brady and Oconnell, 1962***, who used a more specific staining

method with adenosine substrate and the indicator phenol violet to detect PH changes at the sites of ADA activity

However this method is relatively insensitive and has not been found to be suitable for study of ADA in human red Cells.

Spencer et al, (1968) described a new and specific method to study ADA isoenzyme by examination of red lysates after starch-gel electrophoresis. This revealed three generically determined electrophoresis different ADA phenotypes designated ADA 1, ADA2 –1 and ADA2. Family studies indicate that these phenotypes are determined by two alleles, ADA1, and ADA2 at an autosomal locus. ADA1 and ADA2 Phenotype represent the homozygous genotypes ADA1 ADA1 and ADA2 ADA2, respectively and ADA1 ADA2.

Preliminary population data suggest that ADA2 has frequency of about 0.06 in European, 0.04 in Negroes and 0.11 in Asian Indians. ***(Hopkinson et al, 1969***

The behavior of the ADA isoenzyme pattern on storage or after treatment with thiol reagents suggests the occurancy of reactive Sulphydryl Groups in the enzyme molecules.

A new phenotype ADA3-1 was described by ***(Hopkinson et al, 1969)*** who suggested that this is due to the occurrence of a rare allele ADA3, which determines a set of isoenzymes with similar electrophoretic mobility to those determined by ADA2, but with a markedly reduced enzyme activity.

Edwards et al,(1971) described two sets of ADA isoenzymes in human tissue extracts : one set , designated “red cell ADA” was in similar

electrophoretic mobility and also exhibited the same genetic polymorphism as the ADA Isoenzymes of red-cell lysates; The other set of isoenzymes ,designated a,b,c,d and e, was tissue-specific and heterogeneous.

Isoenzyme "a" occurred only in the lung and liver extract, Isoenzyme "e" occurred only in kidney and intestinal extracts, isoenzymes "b, c" And "d" were widely distributed.***(Edwards et al, 1971)***

The "red-cell ADA set of isoenzymes in tissues were also similar in Sulphydryl group reactivity and molecular size (M.W.C.34.000) to the isoenzymes of red-call lysates, and presumably determined by the same genetic locus.

The tissue-specific ADA isoenzymes differ from "red-cell ADA" in Sulphydryl group reactivity and also in molecular size. Isoenzyme "b, c" and "d" were of similar size (M.W.C 280.000), Isoenzyme "e" was larger (M.W.C 440.000), Isoenzyme "a" appeared to be rather labile and it was not possible to assess its molecular size. It is possible that as many as four loci are implicated in determining the structures of the human ADA Isoenzymes "a red –cell ADA locus, a locus determining the "a" isoenzyme a locus for the "e" isoenzyme and a locus for "d". The minor isoenzymes "b" and "c" are postulated secondary isoenzyme of "d". An apparent person to person variation in the relative activities of different ADA isoenzymes occurs in extracts of the same tissue from different people. ***(Edwards et al, 1971)***

Human erythrocyte adenosine deaminase has been purified approximately 800.000 fold to apparent homogeneity using antibody affinity chromatography. The enzyme was shown to be a single

polypeptide chain with an estimated molecular weight of approximately 38.000.The three electrophoretic forms of erythrocyte ADA purified simultaneously by this technique were indistinguishable by sodium dodecylsulfate polyacrylamide gel electrophoresis under reducing conditions ***(Daddona and Kelley ,1977.)***

A protein which specifically complexes with ADA (complexing Protein has been purified to homogeneity from human plasma. This protein was compared with complexing protein isolated from human kidney. The two proteins produce electrophoretically different forms of High molecular weight ADA when combined with the Mr = 36.000 Enzyme monomer from erythrocytes. This difference may, at least in part, be due to the greater sialic acid content of complexing protein from plasma. ***(Schrader et al, 1979).***

By other criteria, including amino acid composition, total carbohydrate content, and subunit structure, the two proteins are quite similar. In addition, plasma complexing protein shows complete cross-reactivity with antikidney complexing protein serum. These results suggest that plasma and kidney complexing proteins are products of the same gene ***(Schrader et al, 1979).***

GENETICS:

The structural gene for ADA is located on chromosome 20 in humans. However, the physical state of the enzyme differs in different human tissues, Where the 38000 Dalton catalytic subunit is associated to variable extents with another high Molecular weight protein referred to as

complexing protein or binding protein ***(Schrader et al ,1979).***the expression which is controlled by genes on human chromosomes 6 and 2.

By immunological techniques, the ratio of catalytic activity of ADA is altered in a number of patient's deficient for that enzyme ***(Carson et al, 1976)*** thus providing evidence that they harbor a mutation in the structural gene for ADA.

ROLE OF ADENOSINE DEAMINASE:

ADA is a key enzyme in the normal catabolic pathway for adenosine nucleotides. This enzyme regulate the amount of adenosine and deoxyadenosine that is catabolized by hypoxanthine and subsequently salvage or oxidized to uric acid ***(Schmalstieg et al, 1977)***

Adenosine and deoxyadenosine generated by the action of nucleotidases on the corresponding nucleotides are substrates of adenosine deaminase ***(Agarwal et al, 1975).***

Although the deamination of adenosine and deoxyadenosine is probably a necessary detoxification process, it is in humans a quantitvely minor contributor to the overall degradation of purines to the usual excreted, uric acid form. Those patients with adenosine deaminase deficiency have normal levels of plasma and urinary urates ***(Miller et al, 1978: Simmonds et al, 1978)*** and only a few percent of their total purine excretion occurs in the form of adenosine deaminase substrates.

Deoxyadenosine and deoxyguanosine, substrates that accumulate in adenosine deaminase (ADA) and purine nucleoside phosphorylase

(PNP) deficiency, respectively, appear to be selectively phosphorylated by lymphoid cells to the corresponding deoxynucleoside triphosphate, resulting in inhibition of DNA synthesis in these cells. Both deoxynuncleosides are far more toxic to cultured T-lymphoblasts than to B-lymphoblasts. Adenosine and deoxyadenosine may have additional lymphotoxic effects mediated by inhibition of essential methylation reactions.**(*Simmonds et al, 1978)***

The first biochemical evidence that deficiency of adenosine deaminase was responsible for immunologic dysfunction observed in enzyme deficient patients was provided by in vitro studies of ***(Polmar et al, 1976)*** on peripheral blood lymphocytes from an adenosine deaminase deficient patient. They observed that while the lymphocytes did not respond to lectin simulation by increasing the incorporation of thymidine into DNA, the introduction of purified calf thymus adenosine deaminase to in vitro mitogenic assay permitted a significant DNA synthesis response.

The role of adenosine deaminase in initial stages of T-cell differention was demonstrated by ***(Shore et al, 1981)*** in patients with adenosine deaminase deficiency.

Incubation of precursor T-cells from adenosine deficient patients directly in contact with thymic epithelial monolayers induced receptors for sheep erythrocytes (E rosettes). ***(Shore et al, 1981)***

Pretreatment of these monolayer with erthro -9- (2.hydroxy -3-monyl) adenine, an inhibitor of adenosine deaminase, prevented differentiation only of adenosine deaminase deficient T-cell precursor,

and this could be restored by providing adenosine deaminase following the incubation with thymic epithelial cells. ***(Shore et al, 1981)***

Adenosine deaminase catalyzes the conversion of adenosine to inosine and deoxyadenosine to deoxyinosine however, in the absence of ADA and the presence of abnormally functioning glycolytic pathway, adenosine and deoxyadenosine are converted obligatory to adenine nucleotides by the action of adenosine kinase and deoxycytidine kinase, respectively. ***(Shore et al, 1981)***

It was found that ATP and cyclic AMP were greatly increased in human blood. Lymphocytes which were deficient in ADA. Certain other purine and pyrimidine nucleotides were elevated but to lesser degree, energy production in there cells may be inhibited by the increase in nucleotides since the ATP: ADA ratio was significantly below normal. Thus it appears that the immunologic deficiency in human ADA deficiency is related to increased nucleotide concentrations in the lymphocytes ***(Schmalstieg et al, 1977).***

ADENOSINE DEAMINASE DEFICIENCY:

Deficiency of the enzyme adenosine deaminase was first reported in two children with severely impaired cellular immunity, lymphopenia, and a variable degree of hypogammaglobulinemia ***(Giblett et al, 1972).***

A subsequent review of 22 children with severe immunodeficiency disease and known ADA status revealed that 13 were ADA deficient, thus

establishing the strength, if not the nature of the association in most instance red cell ADA activity was significantly decreased in both parents of affected children, indicating an autosomal recessive inheritance pattern ***(Meuwissen et al, 1975)***

A hypothesis that a circulating lymphotoxic metabolite might mediate the immunologic disorder in ADA deficiency ***(Meuwissn et al, 1975: Polmar, 1976).***

This supposition was given considerable credence by the observation that transfusion of erythrocytes containing normal ADA activity could increase the lymphocytes counts and restore both cell-mediated and humoral immunity in an ADA deficient child ***(Polmar et al, 1976).***

Subsequent studies have demonstrated the therapeutic efficacy of transfusion therapy or enzyme replacement in some, but not all patients with this disorder **(Polmar, 1979).**

Adenosine deaminase activity is absent in erythrocytes from ADA deficient patients ***(Rosen, 1978)*** and markedly reduced in other tissues ***(Hischhorn et al, 1978).***

Four persons have been identified who had deficient red-cell ADA activity but normal lymphocyte maturation and function ***(Jenkins et al, 1976).***

In each instance, lymphocyte ADA activity was at least 10% of normal and in one instance an unstable mutant enzyme was identified ***(Hischhorn et al, 1979).***

These cases most likely represent genetic mutations at the ADA locus that are district those resulting in a more marked decrease in lymphocyte ADA activity and in immunodeficiency disease.

The sparing effect of residual ADA activity on lymphocytes made it likely that the accumulation of a substrate or of a substrate metabolite the lymphocyte dysfunction in persons with truly deficient lymphocytes

ADA activity have been found in patients with diseases causing impairment of the immune response, as solid tumors ***(Uberti et al, 1976)*** and chronic lympho and myeloprliferactive disorders ***(Tung et al, 1976. Yasmineh et al, 1977)*** and chronic active liver diseases.

INCREASED ADENOSINE DEAMINASE ACTIVITY:

A 45 to 70 fold increase of red cell ADA activity has been observed in kindred with hereditary hemolytic anemia. Patients with this dominantly inherited entity have a mild anemia and decrease of erythrocyte adenine nucleotides to less than 50% of that of comparable reticulocyte-rich blood. The decreased erythrocyte adenine nucleotide concentrations, which appear to be responsible for the hemolytic anemia, may result from the diminished reutilization of adenosine to adenine nucleotides as a result of excessive destruction of adenosine by elevated ADA level. ***(Meier et al; 1976).***

High lymphocyte ADA levels have been found in lymphocytic cells from acute lymphatic leukemia and in blast crisis of chronic lymphatic leukemia ***(Meier et al; 1976).***

High values were also demonstrated in subjects with renal allograft transplants undergoing acute graft rejection. In several diseases were cellular immunity is stimulated, such as typhoid fever ***(Galanti et al, 1981),*** infectious mononucleosis, brucellosis and Mediterranean spotted fever, among others, an increase of serum ADA activity has been described. Cerebrospinal fluid in tuberculous meningitis demonstrates a higher ADA activity than cerebrospinal fluid in other diseases.

Measurement of serum ADA shows elevation in primary liver disease and secondary hepatic neoplasia, it is the most useful single test in portal cirrhosis. ***(Galanti et al, 1981)***

RBC.ADA also elevated in gouty subjects. ***(Galanti et al, 1981).***

Results

Table (1)

Classification of 4 groups according to diagnosis and gender

Diagnosis	No. of Patients		
	Male	Female	Total
Pul. TB	14 (70%)	6 (30%)	20 (40%)
Cancer	8 (80%)	2 (20%)	10 (20%)
Pneumonia	8 (80%)	2 (20%)	10 (20%)
Normal persons	8 (80%)	2 (20%)	10 (20%)
Total	38 (76%)	12 (24%)	50 (100%)

This table shows the 4 groups of patients classified according to gender. 38 (76%) patients were males and 12 (24%) were females.

Out of patients selected, 14 males and 6 females were diagnosed as pulmonary tuberculosis, 8 males and 2 females were diagnosed as bronchogenic carcinoma, 8 males and 2 females were diagnosed as pneumonia, 8 males and 2 females were normal group.

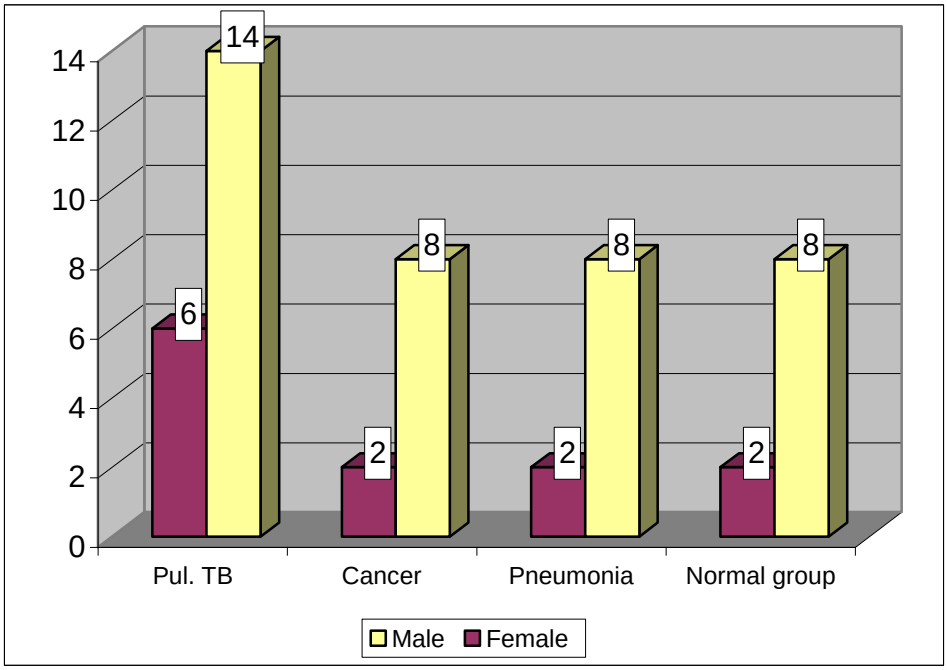


Chart (1) shows the sex distribution among different groups

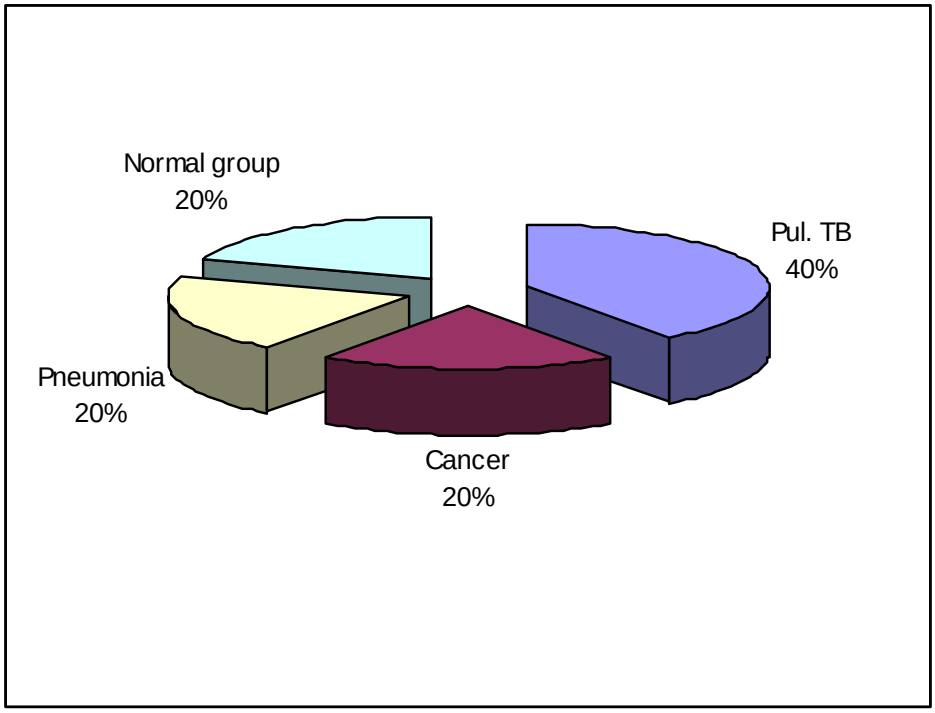


Chart (2): shows groups of patients classified according to diagnosis and percents

Table (2)

Age of subjects in different groups

	No.	Mean	SD	Minimum	Maximum
Pul TB	20	30.85	11.50	16	53
Lung Cancer	10	58.80	6.05	48	68
Pneumonia	10	23.90	5.93	17	34
Normal	10	30.40	11.65	16	53
Total	50	34.96	15.53	16	68

P value < 0.05

The table shows that the age of patients ranged from 16 to 68 years with a mean ±SD 34.96 ± 15.53

Age was ranged from 16 to 53 years with a mean ±SD 30.4 ± 11.56 in group 1, from 16 to 53 years with a mean ±SD 30.85 ± 11.50 in group 2, from 48 to 68 years with a mean ±SD 58.80 ± 06.05 in group 3, and from 16 to 68 years with a mean ±SD 23.90 ± 15.53 in group 4

Table (3)

Clinical data of Subjects

symptoms / Diagnosis	Cough	Expectoration	Dyspnea	Hemoptysis	Chest Pain	Fever
Pulmonary TB	20	20	4	7	6	13
Adenocarcinoma	4	2	4	2	0	0
Squemous Cell Carcinoma	6	5	3	4	3	0
Pneumonia	10	4	7	3	6	10
Normal group	0	0	0	0	0	0
Total and percent	40	31	22	16	15	23
	80%	62%	44%	32%	30%	46%

Total number of patients is (50); The table shows that, as regard the clinical presentation of the patients; cough is the most common symptom in all (40) patients (80%), expectoration was present in (31) patients 62%, Dyspnea was present in (18) 36%, Hemoptysis was present in (16) patients 32%, chest pain was present in (15) patients 30% and fever was present in patients (23) 46%.

PRESENTATION OF SYMPTOMS AMONG THE DIFFERENT GROUPS

Table (4)

Cough

Cough	Pul. TB	Lung Cancer	Pneumonia	Normal
Positive	20	10	10	0
Negative	0	0	0	0

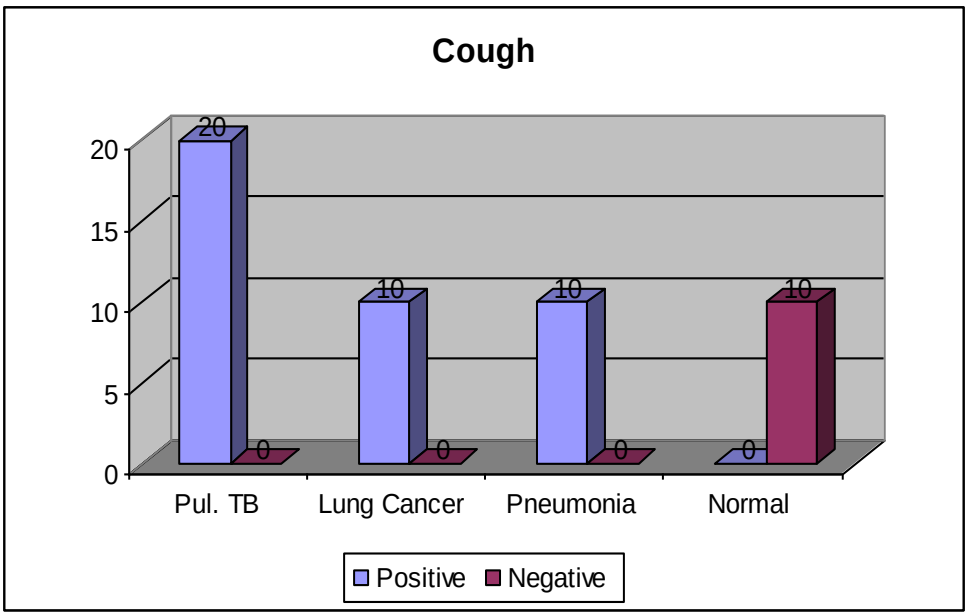


Chart (3): PRESENTATION OF SYMPTOMS AMONG THE DIFFERENT GROUPS

Table (4) and chart (3) show all patients diagnosed as tuberculosis, Pneumonia and Lung cancer was complaining of cough (p value was less than 0.005) which is significant.

Table (5)

Expectoration

	Pul. TB	Lung Cancer	Pneumonia	Normal	Total
Positive	20	7	4	0	19
Negative	0	3	6	10	31

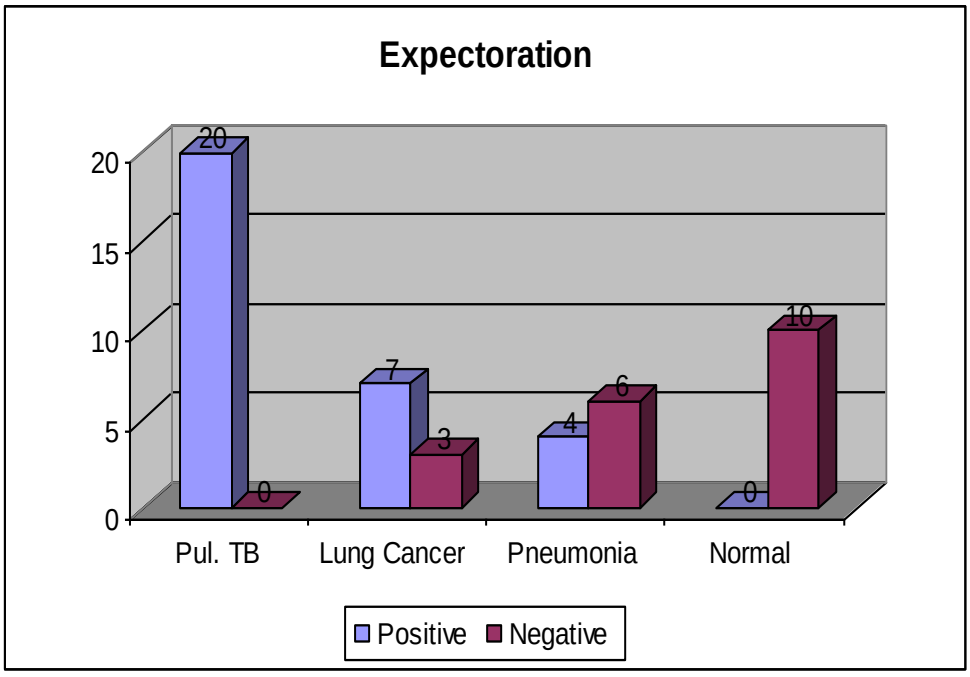


Chart (4): Expectoration among different groups:

Table (5) and chart (4) show that all patients diagnosed as tuberculosis (100%), 7 (70%) of patients diagnosed as lung cancer, 4 (40%) of patients diagnosed as pneumonia were complaining of expectoration (p value was less than 0.005) which is significant.

Table (6)

Dyspnea

	Pul. TB	Lung Cancer	Pneumonia	Normal
Positive	4	7	7	10
Negative	16	3	3	0

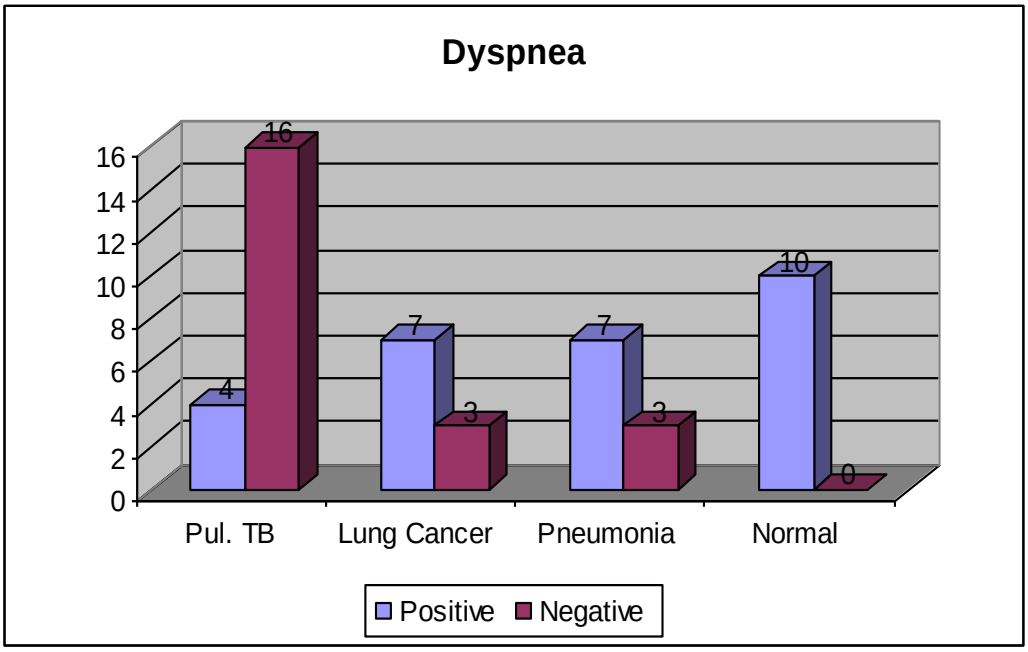


Chart (5): Dyspnea among different groups:

Table (6) and chart (5) show that 4 (20%) of patients diagnosed as tuberculosis, 7 (70%) of patients diagnosed as lung cancer, 7 (70%) of patients diagnosed as pneumonia were complaining of expectoration (p value was less than 0.005) which is significant.

Table (7)

HEMOPTYSIS

	Pul. TB	Lung Cancer	Pneumonia	Normal
Positive	7	6	3	0
Negative	13	4	7	10

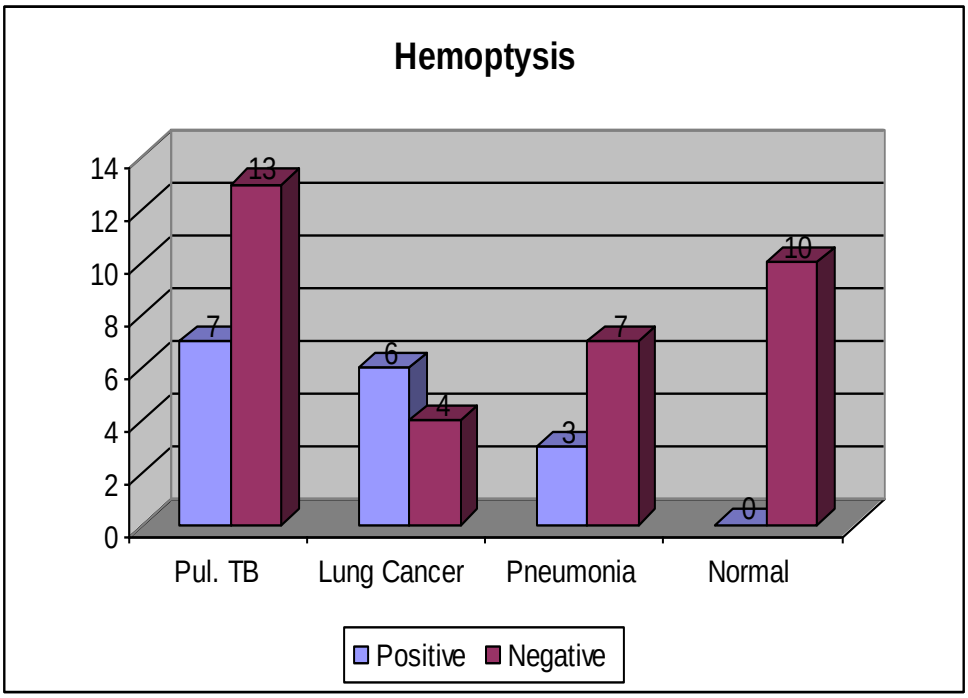


Chart (6): Hemoptysis among different groups:

Table (7) and chart (6) show that 7 (35%) of patients diagnosed as tuberculosis, 6 (60%) of patients diagnosed as lung cancer, 2 (20%) of patients diagnosed as pneumonia were complaining of hemoptysis (p value was more than 0.005) which is insignificant.

Table (8)

Chest Pain

	Pul. TB	Lung Cancer	Pneumonia	Normal
Positive	6	3	6	0
Negative	14	7	4	10

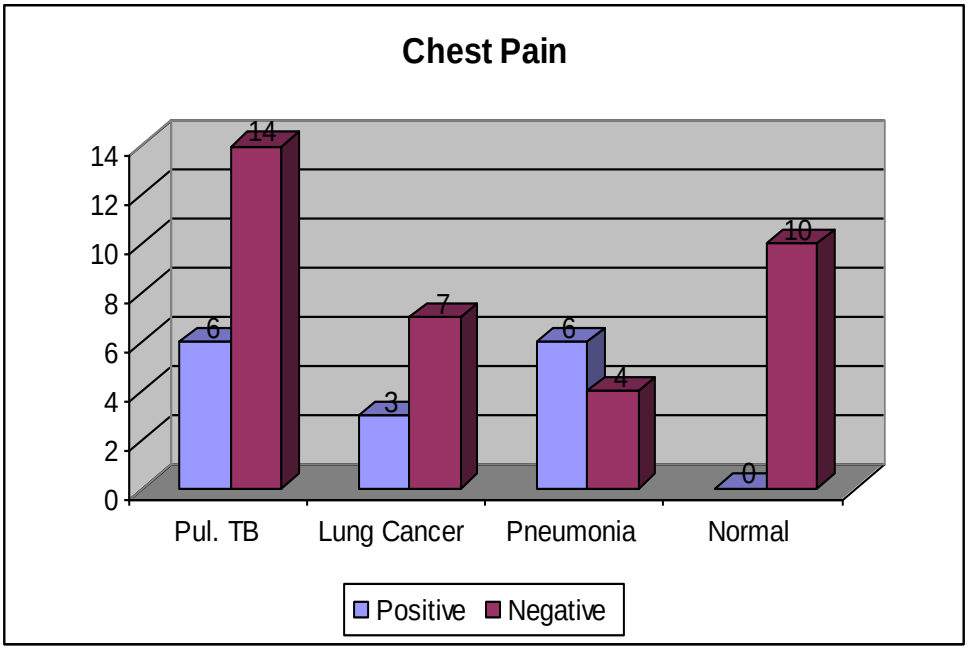


Chart (7): Chest pain among different groups:

Table (8) and chart (7) show that 6 (30%) of patients diagnosed as tuberculosis, 3 (30%) of patients diagnosed as lung cancer, 6 (60%) of patients diagnosed as pneumonia were complaining of chest pain (p value was more than 0.005) which is insignificant.

Table (9)

Fever

	Pul. TB	Lung Cancer	Pneumonia	Normal
Positive	13	0	10	0
Negative	7	10	0	10

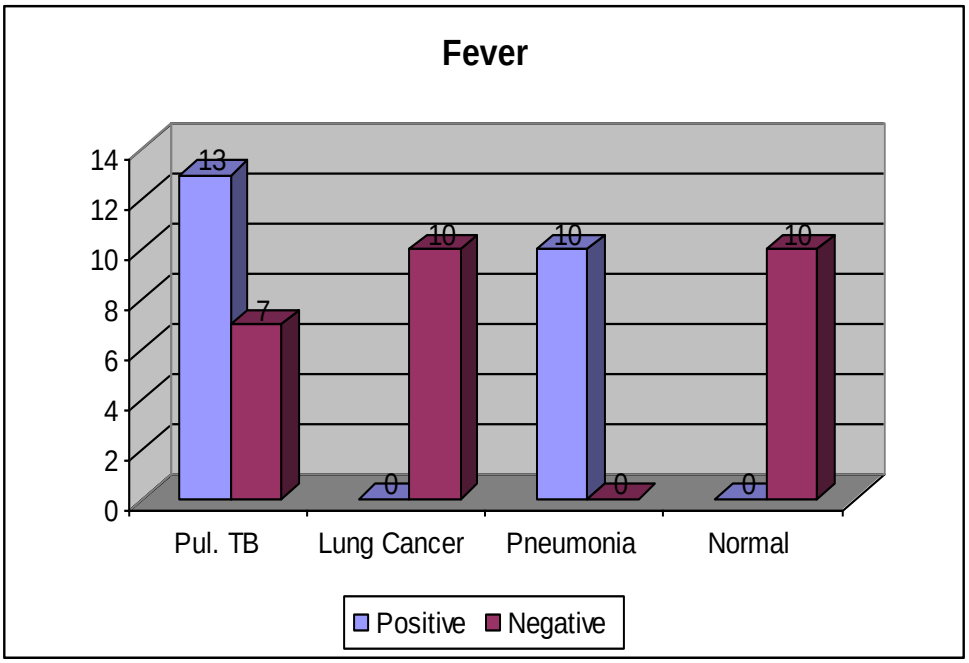


Chart (8): Fever among different groups:

Table (9) and chart (8) show that 13 (65%) patients diagnosed as tuberculosis, no one diagnosed as lung cancer and all patients diagnosed as pneumonia were complaining of fever (p value was less than 0.005) which is significant.

Table (10)

Serum ADA between different groups

	No.	Mean	SD.	Minimum	Maximum
Tb	20	47.5	20.05	25.7	97.4
Adenocarcinoma	4	26.15	5.70	21	34.2
Sq. cell car.	6	18.55	3.95	14	25.3
Pneumonia	10	24.87	8.49	12.1	39
normal	10	23.82	8.24	12.1	37.4

Serum ADA level was (25.7 – 97.4) u/l in tuberculosis patients with mean ± SD 47.5±20.05; (34.2- 21) u/l with mean ± SD 26.15±5.70 in patients with Adenocarcinoma;(14.0 – 25.3) u/l with mean ± SD 18.55± 3.95 in patients with squamous cell carcinoma; (12.1 – 39) with mean ± SD 24.87 ± 8.49 in patients with pneumonia and (12.1 – 37.4) with mean ± SD 23.82 ± 8.24 in normal group.

Table (11)

BALF ADA between different groups

	No.	Mean	SD.	Minimum	Maximum
Tb	20	5.06	1.93	2.70	8.30
Adenocarcinoma	4	1.9	0.53	1.30	2.40
Sq. cell car.	6	2.6	1.47	1.40	5.40
Pneumonia	10	1.77	0.91	0.00	3.10
Normal	10	1.92	0.55	1.10	2.60

BALF ADA level was (2.7 – 8.3) u/l in tuberculosis patients with mean ± SD 5.06±1.93; (1.30- 2.40) u/l with mean ± SD 1.9±0.5 in patients with Adenocarcinoma;(1.4 – 5.4) u/l with mean ± SD 2.6± 1.4 in patients with squamous cell carcinoma; (0.0 – 3.1) with mean ± SD 1.7 ± 0.9 in patients with pneumonia and (1.1 – 2.6) with mean ± SD 1.92 ± 0.5 in normal group.

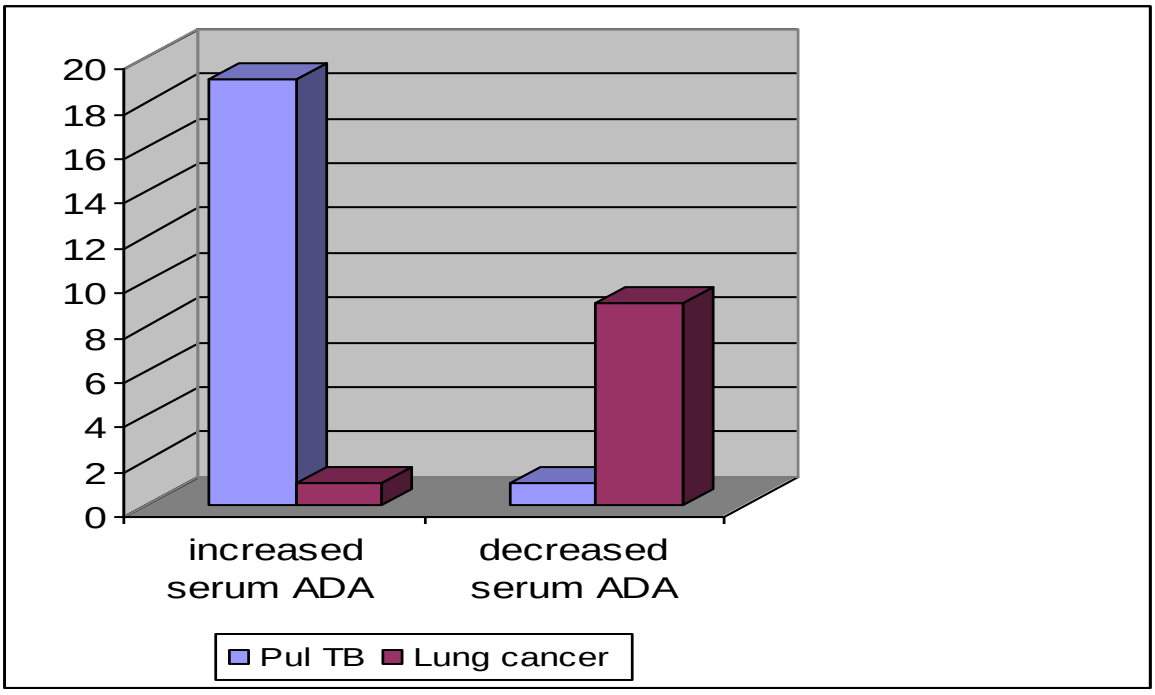
The cut-off points resulted when median values used for the entire group i.e. 50 cases was: For serum ADA level, the group median was 26.2 U/L, For bronchoalveolar lavage fluid (BALF) ADA level, the group median was 2.5 U/L, ADA serum sensitivity was 95%, ADA serum specificity was 83.3%, ADA serum Positive predictive value was 79.2%, ADA BALF sensitivity was 100%, ADA BALF specificity was 83.3% and ADA BALF Positive predictive value was 80%

Table (12)

Comparison of serum ADA in pulmonary tuberculosis and Lung Cancer

		ADA serum	
		≤ 26.2	**> 26.2**
Pul. TB	Count	1	19
	% within ADA Serum grouping	**3.8%**	**79.2%**
Lung cancer	Count	9	1
	% within ADA Serum grouping	**34.6%**	**4.2%**

Chart (9)



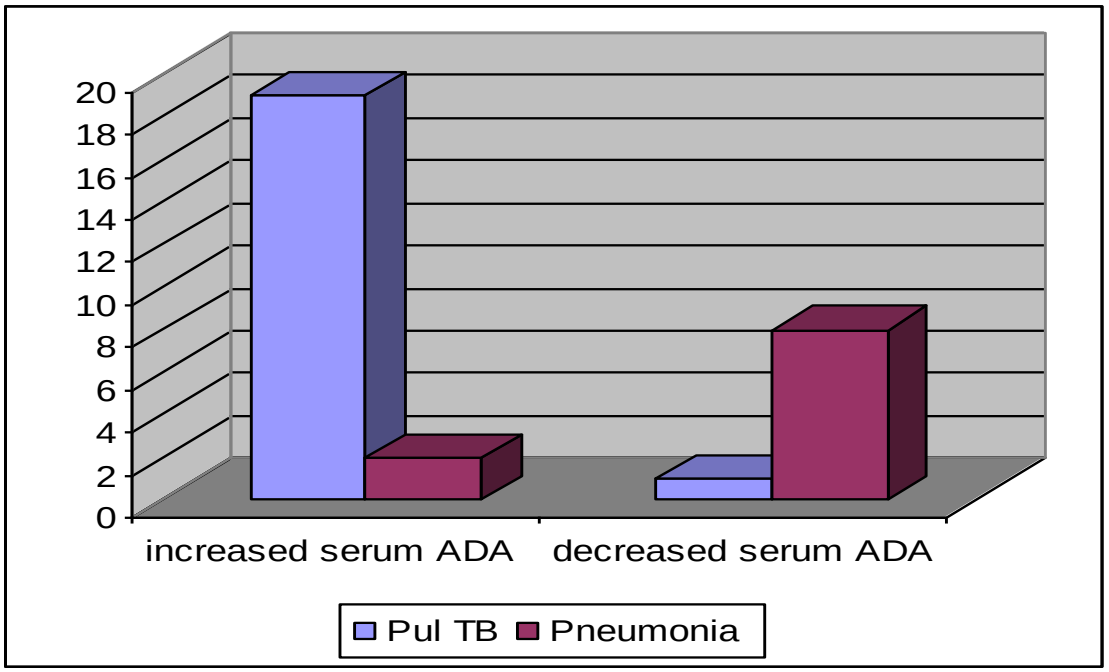
According to the cut off point, the table and the chart show that serum ADA elevated in most patients with pulmonary tuberculosis (19) patients 79.2% from all patients of the selected groups, while serum ADA raise in only one patient with lung cancer, and ADA level decreased in 9 patients.

Table (13)

Comparison of serum ADA in pulmonary tuberculosis and pneumonia

		ADA serum	
		≤ 26.2	**> 26.2**
Pul. TB	Count	1	19
	% within ADA Serum grouping	**3.8%**	**79.2%**
Pneumonia	Count	8	2
	% within ADA Serum grouping	**30.8%**	**8.3%**

Chart (10)



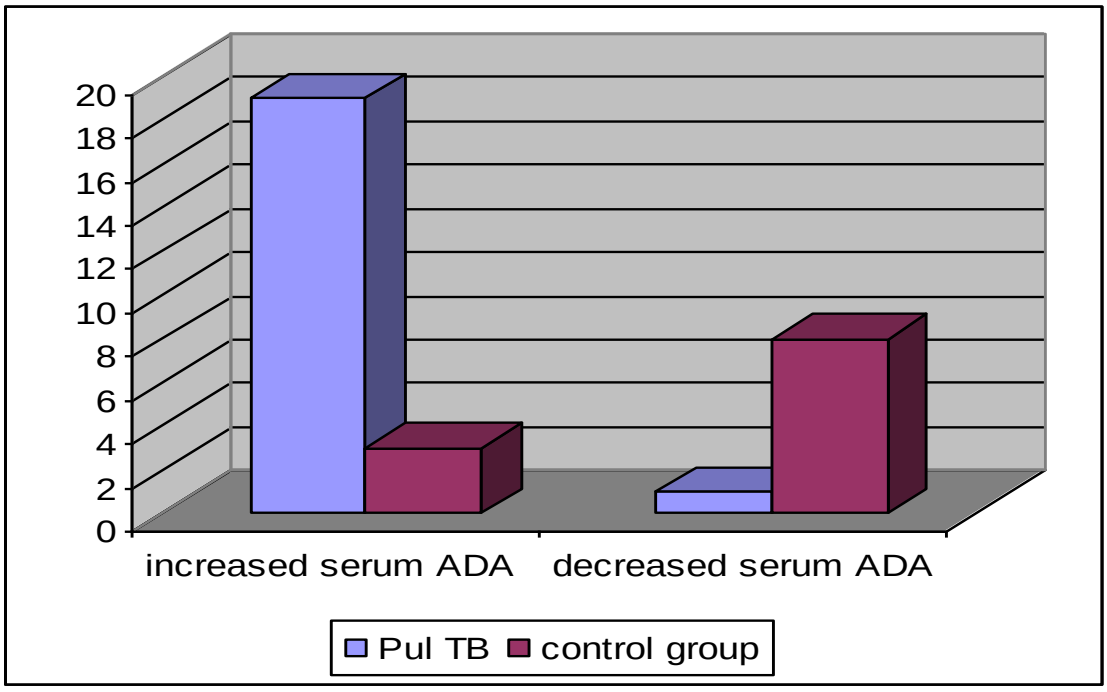
According to the cut off point, the table and the chart show that serum ADA elevated in most patients with pulmonary tuberculosis (19) patients 79.2% from all patients of the selected groups, while serum ADA raise in only two patients with pneumonia, and ADA level decreased in 8 patients.

Table (14)

Comparison of serum ADA in pulmonary tuberculosis and Normal group

		ADA serum	
		≤ 26.2	**> 26.2**
Pul. TB	Count	1	19
	% within ADA Serum grouping	**3.8%**	**79.2%**
Normal	Count	8	2
	% within ADA Serum grouping	**30.8%**	**8.3%**

Chart (11)



According to the cut off point, the table and the chart show that serum ADA elevated in most patients with pulmonary tuberculosis (19) patients 79.2% from all patients of the selected groups, while among the normal group, serum ADA raise in only two, and ADA level decreased in 8 of them.

Table (15)

Comparison of serum ADA in pulmonary tuberculosis

And the other groups

		ADA serum	
		≤ 26.2	**> 26.2**
Pul. TB	Count	1	19
	% within ADA Serum grouping	**3.8%**	**79.2%**
Lung cancer	Count	9	1
	% within ADA Serum grouping	**36.6%**	**4.2%**
Pneumonia	Count	8	2
	% within ADA Serum grouping	**30.8%**	**8.3%**
Normal	Count	8	2
	% within ADA Serum grouping	**30.8%**	**8.3%**

This table shows Comparison of serum ADA in pulmonary tuberculosis and other groups that was 79.2% in pulmonary tuberculosis, 4.2% in lung cancer, 8.3% in Pneumonia and 8.3% in Normal group.

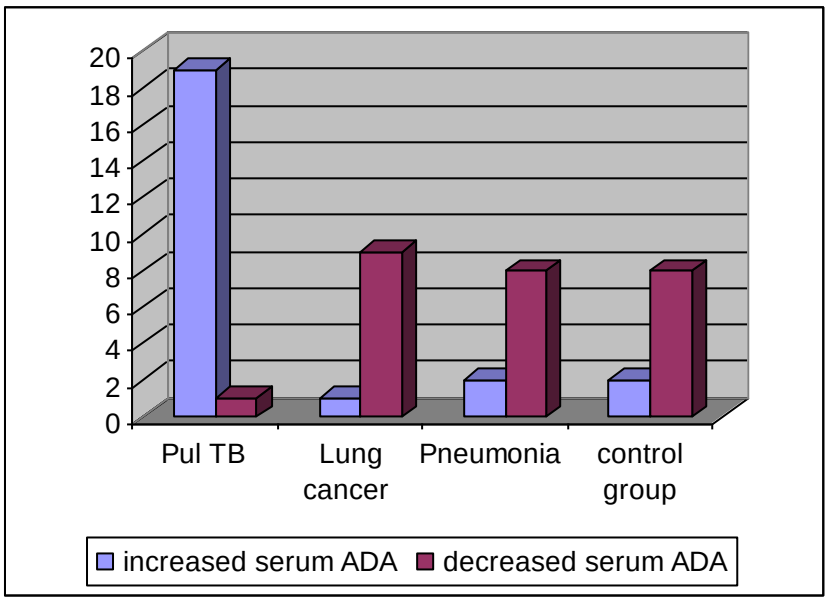


Chart (12) shows the high elevation of serum ADA level in tuberculosis patients in comparison to the different groups of different lung diseases.

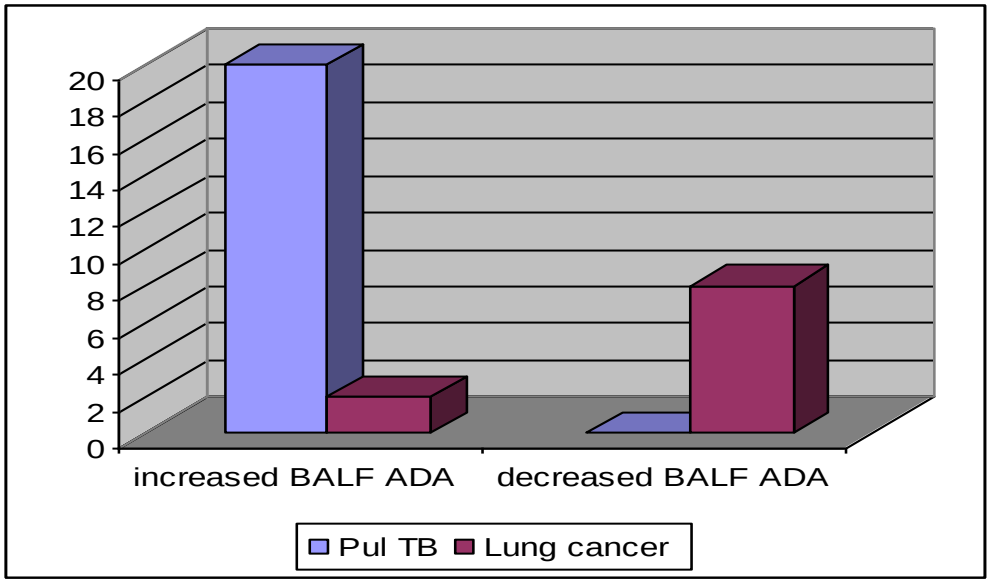
Among 20 patients diagnosed as pulmonary tuberculosis, 19 patients shown elevation of serum ADA level, one patient among 10 patients diagnosed as lung cancer, 2 patients among 10 patients diagnosed as pneumonia shown elevation of serum ADA level and 2 among 10 normal subjects shown elevation of serum ADA level, with sensitivity and specificity 95% and 83.3% respectively.

Table (16)

Comparison of BALF ADA in pulmonary tuberculosis and lung cancer

		ADA BALF	
		≤ 2.5	**> 2.5**
Pul. TB	Count	0	20
	% within ADA BALF grouping	0	**80%**
Lung cancer	Count	8	2
	% within ADA BALF grouping	**32%**	8%

Chart (13)



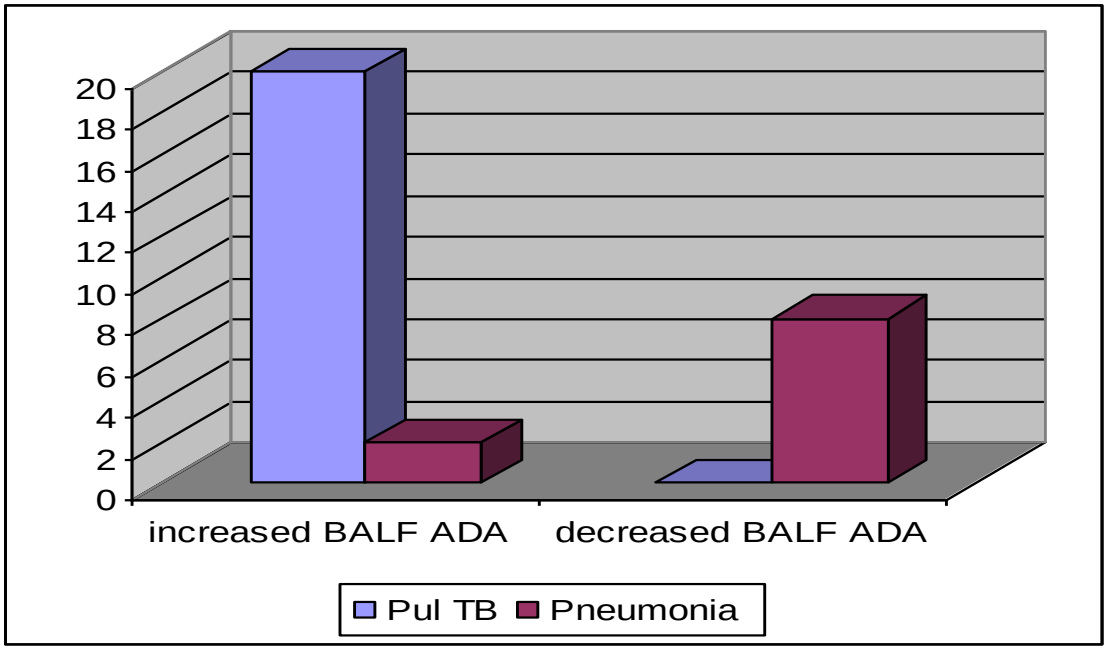
The table and the chart show that the level of ADA in Bronchoalveolar lavage fluid increased in all 20 patients diagnosed as pulmonary tuberculosis with a percent of (80%) of all patients , while among 10 patients diagnosed as Lung cancer while BALF ADA level increased in 2 patients with a percent of (8%) those patients were diagnosed as Adenocarcinoma.

Table (17)

Comparison of BALF ADA in pulmonary tuberculosis and pneumonia

		ADA BALF	
		≤ 2.5	> 2.5
Pul. TB	Count	0	20
	% within ADA BALF grouping	0	**80%**
Pneumonia	Count	8	2
	% within ADA BALF grouping	**32%**	**8%**

Chart (14)



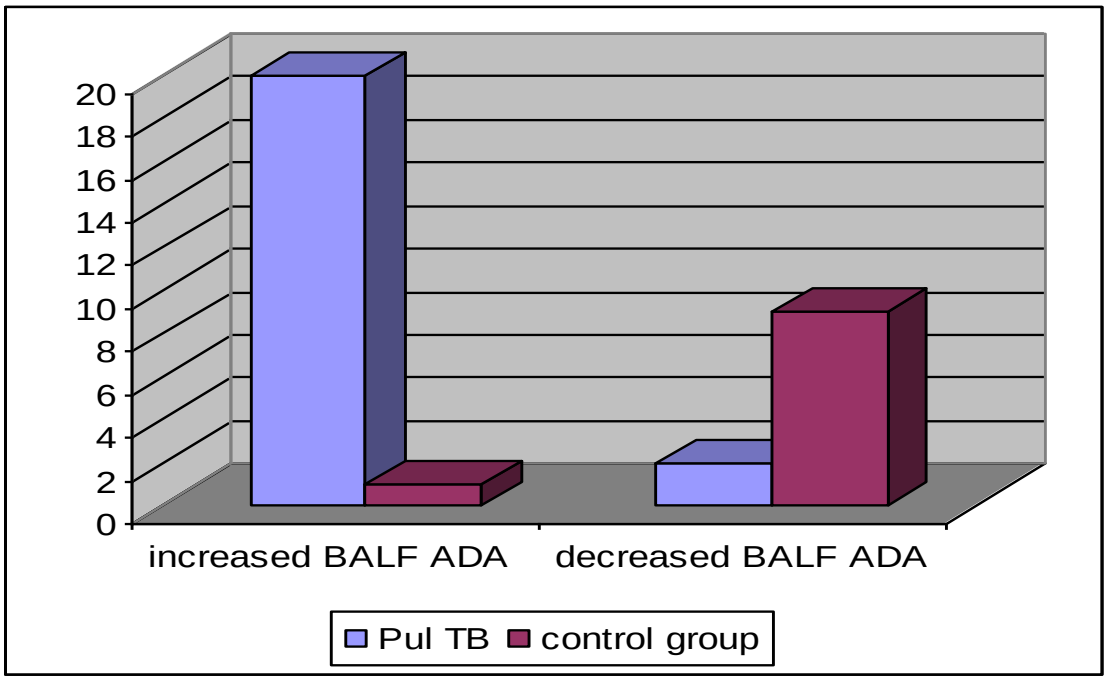
The table and the chart show that the level of ADA in Bronchoalveolar lavage fluid increased in all 20 patients diagnosed as pulmonary tuberculosis with a percent of (80%) of all patients , while BALF ADA level increased in 2 patients among 10 patients diagnosed as pneumonia with a percent of (8%) among all patients.

Table (18)

Comparison of BALF ADA in pulmonary tuberculosis and normal group

		ADA BALF	
		≤ 2.5	> 2.5
Pul. TB	Count	0	20
	% within ADA BALF grouping	0	**80%**
Normal	Count	9	1
	% within ADA BALF grouping	**36%**	**4%**

Chart (15)



The table and the chart show that the level of ADA in Bronchoalveolar lavage fluid increased in all 20 patients diagnosed as pulmonary tuberculosis with a percent of (80%) of all patients , while BALF ADA level increased in only in one among the 10 normal subjects with a percent of (4%) among all patients.

Table (19)

Comparison of BALF ADA in pulmonary tuberculosis and other groups

		ADA BALF	
		≤ 2.5	> 2.5
Pul. TB	Count	0	20
	% within ADA BALF grouping	0	**80%**
Lung cancer	Count	8	2
	% within ADA BALF grouping	**32%**	**8%**
Pneumonia	Count	8	2
	% within ADA BALF grouping	**32%**	**8%**
Normal	Count	9	1
	% within ADA BALF grouping	**36%**	**4%**

This table shows Comparison of BALF ADA in pulmonary tuberculosis and other groups that was 80% in pulmonary tuberculosis, 8% in lung cancer 8 % in Pneumonia and 4 % in normal group.

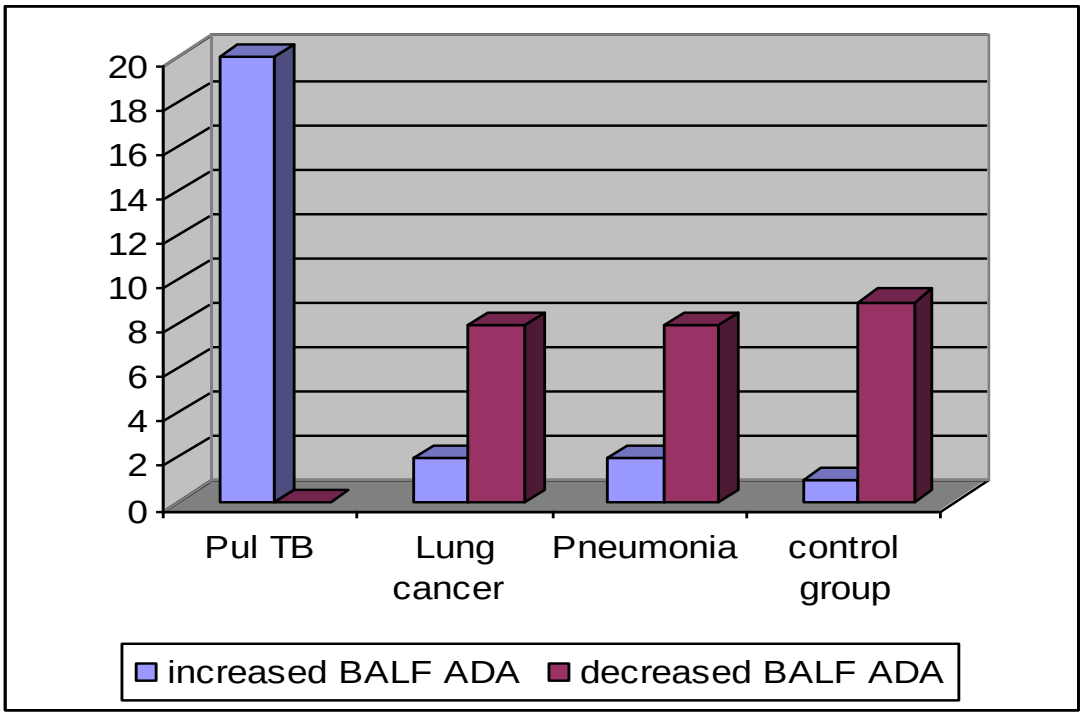


Chart (16) shows the high elevation of BALF ADA in tuberculosis patients from other groups

Among 20 patients diagnosed as pulmonary tuberculosis, 19 patients shown elevation of BALF ADA level, 2 patients among 10 patients diagnosed as lung cancer show increased ADA level in BALF, 2 patients among 10 patients diagnosed as pneumonia shown elevation of BALF ADA level and one among 10 normal subjects shown elevation of BALF ADA level, with sensitivity and specificity 100% and 83.3% respectively.

Table (20)

Blood Lymphocytes in different groups

diagnosis	N	Mean	SD	Minimum	Maximum
Pul. TB	20	37.45	12.64	17	65
Adenocarcinoma	4	32.75	15.17	16	50
Sq. cell carc.	6	27.67	19.40	12	65
Pneumonia	10	29.70	17.11	12	65
Normal	10	29.70	17.11	12	65
Total	**50**	**32.80**	**15.42**	**12**	**65**

Table (21)
Comparison of Lymphocytes between TB and other groups

		Mean difference	Std. error	Sig.
Pul. TB	Adenocarcinoma	4.70	8.51	0.998
	Sq. cell car.	9.78	7.24	0.904
	Pneumonia	7.75	6.02	0.877
	Normal	7.75	6.02	0.877

P value = 0.526

The tables show that the lymphocytes in blood of patients ranged from 17% to 65 % with a mean ±SD 37.45 ± 17.11

Lymphocytes was ranged from 17 to 65 % with a mean ±SD 37.45 ± 12.64 in group 1, from 12 to 50 % with a mean ±SD 32.75 ± 15.17 in group 2, from 12 to 65 years with a mean ±SD 29.70 ± 17.11 in group 3, and from 12 to 65 years with a mean ±SD 29.70 ± 17.11 in group 4

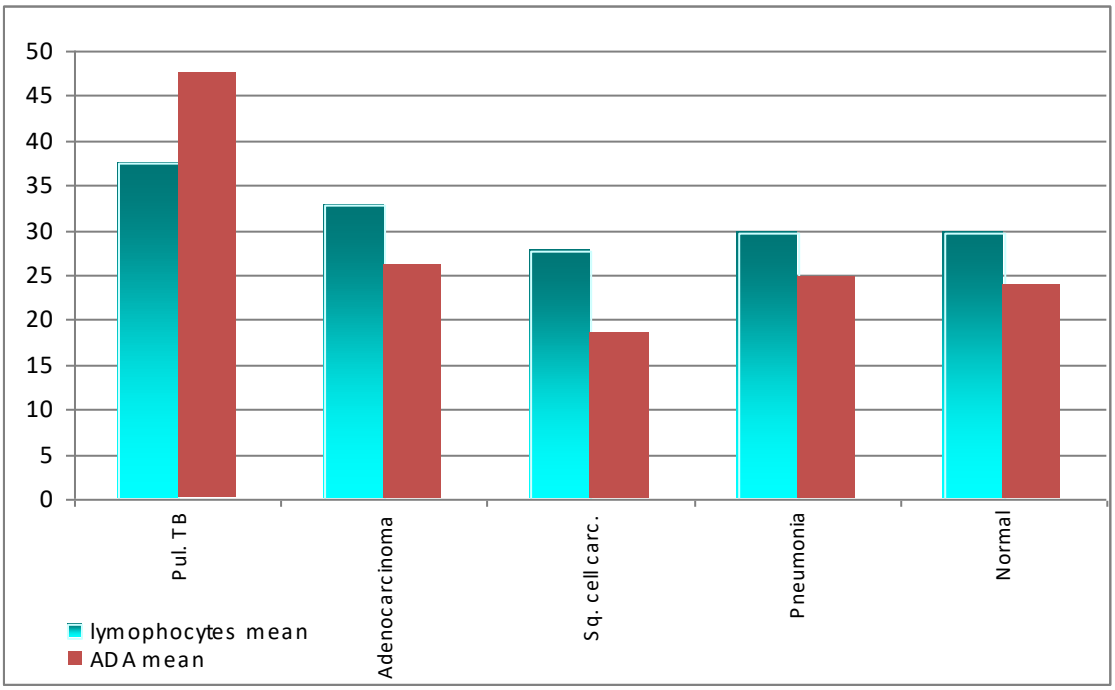
No significant difference was observed in mean lymphocytes activity in blood of different groups among all selected patients.

Table (21)

Blood Lymphocytes in comparison to ADA mean in different settings

diagnosis	N	Mean ± SD	Mean ± SD
Pulmonary. TB	20	**37.45 ± 12.64**	**47.5±20.05**
Adenocarcinoma	4	**32.75 ± 15.17**	**26.15±5.70**
Sq. cell carc.	6	**27.67 ± 19.40**	**18.55±3.95**
Pneumonia	10	**29.70 ± 17.11**	**24.87±8.49**
Normal	10	**29.70 ± 17.11**	**23.82±8.24**

Chart (17)



P value < 0.05

Table (21) and chart (17) show significantly increase the ADA levels in cases of pulmonary tuberculosis due to increase in the lymphocyte cells.

It seems reasonable to regard the high ADA activity in tuberculous patients as a reflection of local activation of T lymphocytes. The level of ADA activity in tuberculosis is higher than any other disease.

ADENOSINE DEAMINASE AND TUBERCULOSIS

IN SERUM

Several reports have suggested the used of serum ADA levels for the diagnosis of pulmonary tuberculosis ***(Segura et al., 1989; Shibagaki et al., 1996; Bhargava et al., 1990; Collazos et al., 1998; Conde et al., 2002).*** The serum ADA levels decrease to normal levels after one month of the initiation of effective treatment ***(Ida et al., 1990; Ishii et al., 1997)***. Highest usefulness of serum ADA is expected in those patients who have higher serum ADA values at presentation. The decrease in serum ADA levels could be due to the normalization of altered lymphocytes turnover induced by tuberculosis.

The measurement of serum ADA activity was useful diagnostic tool in childhood pulmonary tuberculosis. The significantly ($P<0.05$) elevated serum ADA values (74.06±18.5 U/L) were found in children with pulmonary tuberculosis than the healthy children (40.36±12.0 U/L) ***(Kuyucu et al., 1999).*** Children with different forms of tuberculosis like pulmonary, miliary, neurotuberculoma, abdominal and ostearticular tuberculosis have significantly ($P<0.05$) serum ADA values than the healthy individuals ***(Mishra et al., 2000)***. Abnormally high levels of serum ADA activity in all the patients with pulmonary tuberculosis indicated the serum ADA is good diagnostic tool for tuberculosis ***(Ida et al., 1990***). Serum ADA was found a selective marker of immune stimulation in tuberculosis but not in cancer when compared the serum ADA activity of pulmonary tuberculosis patients with the patients of lung

cancer pre-treatment and healthy individuals ***(Kelbel et al., 1995)***. With cutoff values of 30 U/L the specificity, sensitivity, positive predictive values and negative predictive value of the serum ADA was found to be 90, 87, 90 and 66.5%, respectively ***(Lakshmi et al., 1992).***

PERICARDIAL EFFUSION

It is difficult to establish a definitive bacteriological diagnosis of tuberculous pericarditis because of several factors. The most difficult diagnostic case involves the patient with pericarditis is whom the PPD (purified protein derivative) test is positive but tubercle bacilli are not demonstrated in pericardial fluid by histological examination of pericardium or elsewhere in the body in the absence of another cause of pericarditis ***(Desi, 1979 , Martinez- Vasquez et al., 1986; Fowler, 1991, and Koch et al., 1993;***). Because of the difficulty in isolating the causative organism, pericardial tuberculosis is hardly diagnosed ***(Komsuo and Galidela, 1995)***.

A few reports about the use of ADA in the diagnosis of tuberculous pericarditis have been reported ***(Martinez-Vasquez et al., 1986; Koh et al., 1993 and Desi, 1979***). The concentration of adenosine deaminase in T-lymphocytes is inversely proportional to the their degree of differentiation. Since mycobacterium tuberculosis invades the pericardial cavity chiefly through rupture of subpericardial caseous lesions. Bacillus antigens stimulate lymphocytes, which in turn release certain lymphokines that activate macrophages against the mycobacterium and influence the formation of granulomas ***(Kuralay and Comlecki, 1998)***. Recent reports in patients with TB pericarditis have

shown that ADA levels in pericardial fluid are diagnostically useful in early diagnosis of TB pericarditis, particularly when the results of other clinical and laboratory tests are negative ***(Dogan et al., 1999 and Koh et al., 1994)***. Using a cutoff value of ADA activity of 40U/L, the sensitivity and specificity of ADA testing in one series of nine proven patients and five patients with suspected TB pericarditis were 93 and 97% respectively ***(Koh et al., 1994).***

CEREBROSPINAL FLUIDS

Meningeal tuberculosis, the most fearsome manifestation of tuberculosis, presents with fever, headache and altered consciousness. It can easily be missed in insidious forms, particularly in HIV infected patients without evidence of tuberculosis outside the central nervous system ***(Fernandez et al., 1999***). Tuberculosis meningitis is a common cause of morbidity and mortality. With the emergence of AIDS, there is renewed interest in tuberculosis all over the world. The cytochemical analysis of cerebrospinal fluid is the cornerstone for diagnosis but there are diagnostic difficulties in differentiating tuberculosis meningitis from non-tuberculous meningitis. Acid-fast bacilli are seen in less than a quarter of patients and mycobacterium culture is positive in 45-90% of cases. Polymerase chain reaction (PCR), though highly sensitive to identify *mycobacterial* DNA, however it is costly, not widely available and problem with its specificity have been encountered (***Eintracht et al., 2000).***

The determination of ADA activity in cerebrospinal fluid is a reliable and valuable adjunct in differentiating tuberculous from non-

tuberculous meningitis ***(Eintracht et al., 2000***). The study consisted of 11 patients with tuberculous meningitis, 9 with cryptococcal meningitis, 13 with acute bacterial meningitis, 9 with aseptic meningitis and 19 with normal lumber puncture. Using a cut off value of total CSF adenosine deaminase activity of >6 U/L they found the 91% sensitivity and 94% specificity in all the patients by detecting total ADA in tuberculous meningitis and 77.3% compared with those with cryptococcal meningitis or acute meningitis.

Results indicated that ADA of cerebrospinal fluid could differentiate patients with tuberculous meningitis from those with aseptic meningitis or a normal lumber puncture. However, there was overlap for values of ADA between patients with tuberculous meningitis and those with cryptococcal meningitis or acute bacterial meningitis. Using cutoff values of total cerebrospinal fluid ADA activity of 8-20 U/L, various studies have shown the sensitivities of 44-100% and specificities of 75-99% ***(Eintracht et al., 2000; Gambbir et al., 1999 and Pettersson et al., 1992)***. False positive results have been reported with lymphomatous meningitis ***(Petterson et al., 1992).*** These different findings on sensitivity and specificity of ADA in cerebrospinal fluid may be explained by different disease profiles, time of presentation and ages of patients, as lower vales of ADA have been reported from the children with tuberculous meningitis ***(Donal et al., 1996***).

PLEURAL EFFUSION

Tuberculous pleural effusion is thought to result from delayed hypersensitivity reaction that occurs in response to the presence of

mycobacterial antigens in pleural space ***(Leibowitz et al., 1973).*** These mycobacterial antigens may gain access to pleural space from the rupture of a small, subpleural caseous focus (***Stead et al., 1995).*** Tuberculous pleural effusion has been described as an acute granulomatous pleuritis occurring as a sequel to recent tuberculous infection in young adults and children who usually do not have roentgenographically apparent parenchymal tuberculosis ***(Levine et al., 1968; Stead et al., 1968; Khan et al., 1977; Sibley, 1950; Frostad, 1944)***. However it is now known that tuberculous pleural effusion may occur in older adults and patients with classic reactivation tuberculosis (***Epstein et al., 1987).***

Diagnosis of tuberculous pleural effusion is difficult and remains a common clinical challenge because all the classic findings of a lymphocytic exudative pleural effusion, pleural granulomata, and cutaneous sensitivity to pleural protein derivative (PPD) may not be present or available to the clinician. Pleural fluid and pleural biopsy, which grow *Mycobacterium Tuberculosis*, have the highest specificity, but their diagnostic utility is limited by their sensitivity. As a result, pleural biopsy and pleural fluid culture findings are negative ***(Bothamley, 1995; Roth, 1999).***

Adenosine deaminase (ADA) has gained increasing popularity as a diagnostic test for tuberculous pleuritis since 1973, especially in countries where the prevalence of tuberculosis is high. It caries 90-100% sensitivity ***(Raintawan et al., 1999; Valdes et al., 1996; Burgess et al., 1996; Aggarwal et al., 1999)*** and is inexpensive ***(Roth, 1999)***. The ADA measurement is used commonly in European and Asian countries where there is a higher incidence of tuberculosis ***(Ferrer et al., 1996).*** In regions

with a high prevalence of tuberculosis and in patient groups with a low risk of other causes of pleurisy, especially among patients with a low probability of neoplasia who may also have high ADA level, the positive predictive value of this marker (ADA) is increased ***(Burgess et al., 1995).*** The problem with using the ADA assay in a population with a lower incidence of tuberculosis is that the positive predictive value decreases, so there is a higher likelihood that a test would give false-positive results ***(San Jose et al., 1999; Sharma et al., 2001).*** One study showed that ADA level, especially when combined with differential cell counts and lymphocyte/neutrophil ratios, remains a useful test in the diagnosis of tuberculous pleuritis.

Several studies have suggested that an elevated pleural fluid ADA level predicts tuberculous pleuritis with a sensitivity of 90-100% and a specificity of 89-100% when the Giusti method is used ***(Gelani et al., 1999; Jimenez et al., 2002; Hamada et al., 1998)***. The reported cutoff value for ADA (total) varies from 47 to 60 U/L ***(Perez-Rodriguez et al., 1999; Valdes et al., 1993 and Reechaipichitkul et al., 2001).***

ASCITIC FLUID

Peritoneal tuberculosis results from reactivation of latent tuberculosis foci in the peritoneum, seeded previously from haematogenous spread from primary infection in the lungs. Tuberculosis peritonitis is associated with active tuberculosis in 4 to 21% of cases ***(Marshall, 1993).*** Tuberculosis peritonitis is divided into three types ***(Dwividi et al., 1990***) the wet type is the most common type and is characterized by large amounts of free or loculated viscous fluid; second

the fibrotic-fixed type is less common and has large omental masses, matted and tethered bowl loops and mesentery and occasionally loculated ascities; third the dry or plastic type is characterized by caseous nodules, fibrous peritoneal reaction and dense adhesion (***Jadvar et al., 1997.***

Tuberculous peritonitis is a significant problem in the countries with high incidence of tuberculosis. Peritoneal involvement in tuberculous infection is frequently associated with cirrhosis and immunodeficient ***states (Alvarez and McCabe, 1984; Burack et al., 1960; Karmy et al., 1977; Borhanmanesh et al., 1986 and Gilinsky et al., 1983).*** The available diagnostic tests for tuberculous peritonitis include paracenthesis with acid-fast smears and culture, laparoscopy with directed biopsy, blind percutaneous peritoneal biopsy and diagnostic laparoscopy. However, laparoscopy is invasive, expensive and associated with complications. It may also be used up to 3% of patients (***Lado-Lado et al., 2002).*** A new test measuring adenosine deaminase activity in the ascitic fluid has been used with promising results ***(Dwividi et al., 1990).***

Ascitic fluid ADA activity has been proposed as a useful diagnostic test for diagnosis of tuberculous peritonitis. Various reports have suggested 100% sensitivity for diagnosis of peritoneal tuberculosis with specificities in the range of 92-100% ***(Dwividi et al., 1990; Fernandez-Rodriguez et al., 1991; Ribera et al., 1991; Voigt et al., 1997, Binder, 1997 and Gupta et al., 1992***). A cutoff value of >33 U/L eliminates false positive tests resulting from cirrhosis or malignancy ***(Dwividi et al., 1990; Fernandez-Rodriguez et al., 1991).***In countries with high incidence of tuberculosis and in high-risk patients, measurement of ADA in ascitic fluid, should be used as a useful

screening test for tuberculosis ***(Binder, 1997 and Gimenez et al., 1992)*** but populations with low prevalence of tuberculosis and high prevalence of cirrhosis, ascitic fluid ADA activity has good accuracy but poor sensitivity and imperfect specificity ***(Hildebrand et al., 1996).***

In the regions with high incidence of tuberculosis and diagnostic procedures are expensive, ADA appears to a useful marker for early diagnosis of tuberculosis. The sensitivity and specificity of ADA depends on the prevalence of tuberculosis in the population. The differences between the reported ADA levels are due to the different methods of ADA measurement.

Discussion

Tuberculosis is a disease of great antiquity. What were almost certainly tuberculous lesions have been found in the vertebrae of Neolithic man in Europe and on Egyptian mummies dating possibly from as early as 3700 BC. ***(Morse D, et al, 1964).***

Tuberculosis has become the most important communicable disease in the world, with over 8 million cases of pulmonary tuberculosis occurring each year, 95% of which are in developing countries ***(World Health Organization 2002,).***

As tuberculosis has declined in the developed world, there has been an associated decrease in experience and awareness of the disease, as reflected by increasing numbers of diagnoses of tuberculosis made after, rather than before death***. (Horne NW, 1984 and Rowinska E., et al, 1995).***

The problem in diagnosing tuberculosis is that no symptom or sign is exactly typical of it. The presence of infection in the body does not necessarily mean disease. From the disease point of view, recovering the bacilli from patient's specimen (by smear/culture) is specific but not sensitive***.(G H Swingler, 2005)***

A Rapid and accurate diagnosis of symptomatic patients is a cornerstone of global tuberculosis normal strategies. Remarkable progress has recently been made upgrading the speed and quality of mycobacteriology diagnostic services in developed countries, but for most of the world where T.B is a large public health burden those gains are still unrealized. **.** ***(G* H Swingler, 2005*)***

Deficiencies in current case-finding tools in disease endemic countries have made it difficult to ensure access to good diagnostics at all health service levels, leaving many patients undiagnosed.

Additionally, in well-established TB control programs where diagnostic access has been ensured, efforts to interrupt disease transmission have been hampered by the insensitivity and late detection of smear microscopy. ***.(* G H Swingler, 2005*)***

In 1970, serum ADA level was first used as a serological diagnostic marker for lung cancer. It was not until 1978, when ADA was found to be useful in diagnosing tuberculous pleurisy ***(Fontan-Bueso, et al., 1988; Porcel and Vives, 2002).***

The ADA assay may be used in adjunction with other methods in the diagnosis and follow up of tuberculosis with high sensitivity, specificity and ease in applicability and specimen collection ***(Canbolat O. et al, 1999).***

Serum ADA level is valuable in identifying those patients in whom the diagnosis of pulmonary T.B should be actively considered (***Lakshmiv et al, 1992).***

Patients with pulmonary tuberculosis had significantly higher ADA level in BALF than patients with non- tuberculosis lung diseases ($P< 0.001$). High Broncho-alveolar lavage fluid (BALF) ADA level in pulmonary tuberculous patients suggests increased local production, in contrast, in those patients BALF ADA level is not significantly higher than in patients with interstitial lung diseases, so BALF ADA level seems to be useful tool in the differentiation of tuberculosis from other lung diseases ***(Orphanidou et al, 1998).***

ADA serum levels were statistically significantly increased in T.B patient when compared to lung cancer patients and normals and did not differ between normals and the tumour groups , this conclude that serum ADA is a selective marker of immune stimulation in tuberculosis but not in lung cancer .***(Kelbelc et al, 1995).***

Discussion

Serum ADA levels in patients with pulmonary tuberculosis decrease during the initial months of effective treatment, perhaps this decrease might reflect the normalization of altered lymphocytes turnover induced by T.B. ***(Collazos J. et al, 1998***)

Highest BAL ADA observed in pulmonary tuberculosis patients suggests an increased local production and differentiate pulmonary tuberculosis from other lung diseases ***(Albera et al, 1993)***

The serum ADA level can be used for the differential diagnosis of pulmonary diseases. ***(Bansal S K. et al, 1991)***

Simultaneous ADA analysis of the blood and BALF may be of diagnostic value in cases suspected of having tuberculosis as yet undiagnosed by other means ***.(Pushpakom R. et al, 1990)***

The aim of this study is to assess the role of adenosine deaminase enzyme (ADA) level in serum and broncho alveolar lavage fluid (BALF) in the diagnosis of pulmonary tuberculosis and to differentiate it from other lung diseases.

This study was carried out on (50) patients, selected from chest department, Cairo University & Giza chest hospital;

Those patients were classified into (4) groups:

Group (I): (20) patients with sputum positive for AFB. Group (2): (10) patients with Bronchogenic carcinoma, diagnosed clinically, radiologically & histopathologically. Out of these patients (4) patients were diagnosed as adenocarcinoma and (6) patients were diagnosed as squamous cell carcinoma histopathologically. Group (3): (10) patients with Pneumonia. They were diagnosed clinically and radiologically. Group (4): (10) normal persons.

ALL Patients were subjected to the following: -

(1) Thorough history taking and clinical examinations.

(2) Plain chest x-ray (postero-anterior & lateral view).

(3) Sputum for AFB.

(4) Routine laboratory Investigations including:

CBC & Differential count.

Liver & Renal Function Tests.

(5) ADA in serum & BAL fluid

Some patients were excluded according to these criteria:

- Patients with Diabetes Mellitus.
- Immunocompromised patients.
- Patients on corticosteroids.
- Patients with hepatic and renal impairment.

Out of the 50 patients selected, 38 (76%) of patients were male and 12 (24%) were female. the age of patients ranged from 16 to 68 years with a mean ±SD 34.96 ± 15.53.

(16 to 53 years with a mean ±SD 30.4 ± 11.56 in group 1 and from 16 to 53 years with a mean ±SD 30.85 ± 11.50 in group 2 and from 48 to 68 years with a mean ±SD 58.80 ± 06.05 in group 3 and from 16 to 68 years with a mean ±SD 23.90 ± 15.53 in group 4).

The most prevalent complaint among the 50 patients were cough as it was found in all (40) patients, then expectoration was found in 31 patients (62%) , dyspnea in 18 patients (36%), Heamoptysis in 16 patients(32%), chest pain in 15 patients (30%), fever in patients 23 (46%) and toxemic manifestations in 14 patients (28%).

ADA level was evaluated in the serum and broncho alveolar lavage fluid (BALF) of those patients.

EVALUATION OF SERUM ADA LEVEL IN DIFFERENT GROUPS:

Serum ADA level was measured among four groups the results were:

Serum ADA in tuberculous group:

Serum ADA level was (25.7 – 97.4) u/l in tuberculosis patients with mean ± SD 47.5±20.05

Serum ADA in cancer group:

Serum ADA level was (21 - 34.2) u/l with mean ± SD 26.15±5.70 in patients with adenocarcinoma ;(14.0 – 25.3) u/l with mean ± SD 18.55± 3.95 in patients with squemous cell carcinoma

Serum ADA in pneumonic group:

Serum ADA level was (12.1 – 39) with mean ± SD 24.87 ± 8.49 in patients with pneumonia

Serum ADA in normal group:

Serum ADA calculation was (12.1 – 37.4) with mean ± SD 23.82 ± 8.24 in normal group.

The cut-off points obtained from the median values for all the group i.e. 50 cases

For serum ADA cut off point was 26.2, ADA serum sensitivity and specificity were 95%, 83.3% respectively with positive predictive value 79.2%.

EVALUATION OF BALF ADA LEVEL IN DIFFERENT GROUPS:

BALF ADA level was measured among the four groups the results were:

BALF ADA in tuberculous group:

BALF ADA level was (2.7 – 8.3) u/l in tuberculosis patients with mean ± SD 5.06±1.93

BALF ADA in cancer group:

BALF ADA level was (1.30- 2.40) u/l with mean ± SD 1.9±0.5 in patients with Adenocarcinoma ;(1.4 – 5.4) u/l with mean ± SD 2.6 ± 1.4 in patients with squamous cell carcinoma

BALF ADA in pneumonic group:

BALFADA level was (0.0 – 3.1) with mean ± SD 1.7 ± 0.9 in patients with pneumonia

BALF ADA in normal subjects:

BALF ADA calculation was (1.1 – 2.6) with mean ± SD 1.92 ± 0.5 in normal subjects.

The cut-off points obtained from the median values for all the group i.e. 50 cases

For BALF ADA, cut off point was 2.5, BALF ADA sensitivity and specificity were 100%, 83.3% respectively with positive predictive value 80%.

Serum ADA

Several studies were carried out have suggested the use of serum ADA levels for the diagnosis of pulmonary tuberculosis ***(Collazos et al., 1998; Baganah et al., 1990; Bansal et al., 1991; Segura et al., 1989; Shibagaki et al., 1996; Bhargava et al., 1990; Conde et al., 2002)***.

The serum ADA levels decrease to normal levels after one month of the initiation of effective treatment ***(Ida et al., 1990; Ishii et al., 1997)***.

Highest usefulness of serum ADA is expected in those patients who have higher serum ADA values at presentation.

The decrease in serum ADA levels could be due to the normalization of altered lymphocytes turnover induced by tuberculosis.

The significantly ($P<0.05$) elevated serum ADA values (74.06±18.5 U/L) were found in children with pulmonary tuberculosis than the healthy

children (40.36±12.0 U/L) ***(Kuyucu et al., 1999)***. Children with different forms of tuberculosis like pulmonary, military, neurotuberculoma, abdominal and ostearticular tuberculosis have significantly (P<0.05) serum ADA values than the healthy individuals ***(Mishra et al., 2000***).

Abnormally high levels of serum ADA level in all the patients with pulmonary tuberculosis indicated the serum ADA is good diagnostic tool for tuberculosis ***(Ida et al., 1990)***.

Serum ADA was found a selective marker of immune stimulation in tuberculosis but not in cancer when compared the serum ADA level of pulmonary tuberculosis patients with the patients of lung cancer pre-treatment and healthy individuals ***(Kelbel et al., 1995)***. With cut off values of 30 U/L the specificity, sensitivity, positive predictive values and negative ***J. Med. Sci., 3 (1): 30-45, 2003,*** predictive value of the serum ADA was found to be 90, 87, 90 and 66.5%, respectively ***(Lakshmi et al., 1992).***

ADA isoenzymes have been suggested to increase the overall diagnostic value of ADA determination ***(Ungerer et al., 1994; Gorguner et al., 2000; Gakis, 1995; Gakis, 1996; Gakis et al., 1991; Ungerer et al., 1988 and Kurata et al., 1992)***.

ADA isoenzymes pattern appears to be a reflection of the difference in immune response and of the corresponding predominant cell population in the body fluid.

Another study reported significantly (P<0.05) higher level of total ADA, ADA-1 and ADA-2 in the sera of patients with pulmonary tuberculosis than those of healthy persons. Close correlation between the level of ADA-2 and lymphocyte subpopulation in pulmonary tuberculosis was found and levels of the level of total ADA, ADA-1 and ADA-2 decreased significantly (P<0.05) in the sera of the patients after three months of effective treatment ***(Ishii et al., 1997).***

Discussion

The results of this study showed that patients with pulmonary tuberculosis had significantly higher ADA level in serum and BALF than patients with non- tuberculosis lung diseases (lung cancer , pneumonia) and normal persons (P< 0.001) with cut off point obtained was ; in serum ADA level was 26.2, with sensitivity and specificity were 95% and 83.3% respectively and positive predictive value was 79.2% and in BALF ADA level, the cut of point was 2.5, with sensitivity and specificity were 100% and 83.3% respectively and Positive predictive value was 80%

ADA serum levels were statistically significantly increased in T.B patient when compared to patients with non- tuberculosis lung diseases and normal persons and did not differ between normal persons and the other lung diseases groups , this conclude that serum and BALF ADA level is a selective marker of immune stimulation in tuberculosis but not in non- tuberculosis lung diseases

The results of present study were in agreement with those of ***Canbolat O. et al, (1999), Lakshmiv et al, (1992), Orphanidou et al, (1998), Kelbelc et al,(1995), Collazos J. et al, (1998) ,Albera et al, (1993) ,Bansal S K. et al, (1991).and Pushpakom R. et al, (1990)*** , so we can use serum and BALF ADA level to differentiate between highly suspect pulmonary tuberculosis and pneumonia or lung cancer.

That ADA rises in serum and BALF of patient have pulmonary tuberculosis, so, we can use the measurement of ADA in serum and BALF to differentiate pulmonary tuberculosis from other lung diseases.

SUMMARY AND CONCLUSION

Tuberculosis still one of the major health problems in the world with more than 7 million new cases and 3 million deaths each year. ***(Murray et al., 1990)***

The present study was done to assess the role of adenosine deaminase level in serum and Broncho Alveolar Lavage in diagnosis of pulmonary tuberculosis.

The study was carried out on 50 patients selected from chest department, Cairo University and Giza chest hospital. They were divided into 4 groups according to the diagnosis, group (1): tuberculosis patients positive for AFB by microscopic examination, group (2): cancer patients, confirmed histopathologically. Group (3): pneumonia patients and group (4): normal persons.

All patients were subjected to thorough history taking and clinical examination, Plain chest x-ray (Postero anterior and Lateral View), Sputum examination for Acid Fast Bacilli (AFB), Routine laboratory Investigations including: Complete Blood Count & differential count, liver & renal function tests and Adenosine deaminase (ADA) in serum & broncho alveolar lavage fluid BALF.

Some patients were excluded according to these criteria:

- Patients with Diabetes Mellitus
- Immunocompromised patients
- Patients on corticosteroids
- Patients with hepatic and renal impairment.

Out of the 50 patients selected, 38 (76%) of patients were male and 12 (24%) were female. the age of patients ranged from 16 to 68 years with a mean ±SD 34.96 ± 15.53.

The most prevalent complaint among the 50 patients were cough as it was found in all (40) patients, then expectoration was found in 31 patients (62%) , dyspnea in 18 patients (36%), Heamoptysis in 16 patients(32%), chest pain in 15 patients (30%), fever in patients 23 (46%) and toxemic manifestations in 14 patients (28%).

The results of this study showed that patients with pulmonary tuberculosis had significantly higher ADA level in serum and BALF than patients with non- tuberculosis lung diseases (P< 0.001) with cut off point obtained, in serum ADA level was 26.2 u/l, with sensitivity and specificity were 95% and 83.3% respectively and Positive predictive value was 79.2% and in BALF ADA level, the cut of point was 2.5 u/l, with sensitivity and specificity were 100% and 83.3% respectively and Positive predictive value was 80%

The test specificity was equal in both serum and broncho alveolar lavage fluid (83.3%) but the sensitivity was higher in BALF ADA level 100% versus serum ADA (95%).

The cost of ADA was very expensive and not suitable for every patient if it is used as routine investigation.

Examination of sputum for AFB is still the recommended test and routine investigation for diagnosis of pulmonary tuberculosis in Egypt.

ADA serum and BALF ADA levels were statistically significantly increased in T.B patient when compared to patients with non- tuberculosis lung diseases and normal persons and did not

differ between controls and the other lung diseases groups , this conclude that serum and BALF ADA is a selective marker of immune stimulation in tuberculosis but not in non- tuberculosis lung diseases

Conclusion

The role of adenosine deaminase ADA in the diagnosis of pulmonary tuberculosis was revealed significantly increase ADA level in serum and BALF of patients with pulmonary tuberculosis than those with cancer, pneumonia and normal persons.

Recommendations

Adenosine deaminase in still not used as routine investigation for diagnosis of pulmonary tuberculosis for these reasons:

1. Adenosine deaminase enzyme in serum would require improved specificity in order to be used as a screening test for routine diagnosis of pulmonary tuberculosis.
2. It has to be evaluated on a large number of patients with fresh pulmonary tuberculosis not receiving antituberculous treatment to be evaluated properly.
3. ADA level is increasing in serum of patients in many diseases rather than tuberculosis.
4. It is very expensive in comparison to direct sputum examination for acid fast bacilli.
5. Broncho alveolar lavage is an invasive technique and not available in every chest unit.

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REVIEW OF LITERATURE

INTRODUCTION

TUBERCULOSIS

ADENOSINE DEAMINASE

TUBERCULOSIS
AND
ADENOSINE DEAMINASE

PATIENTS AND METHODS

RESULTS

DISSCUSSION

SUMMARY, CONCLUSION AND RECOMMENDATIONS

REFERENCES

APPENDIXES

الملخص العربى

الملخص العربي

الدرن الرئوي مرض بكتيري ينتشر عن طريق إستنشاق الهواء المحمل بميكروب الدرن. وتشير إحصائيات الأمم المتحدة إلى أن تسعة ملايين شخص يصابون بالدرن سنوياً، يتوفى منهم ثلاثة ملايين مريض كل عام.

ويعتمد تشخيص الدرن الرئوي على الطرق المعملية والحالة المرضية للمصاب. ومن أهم هذه الطرق المعملية وأكثرها إستخداماً على الإطلاق هو الفحص المجهري لعينات البصاق، إلا أن هذه الطريقة تفقد عدداً من المرضى دون تشخيص مما يجعلهم مصدر عدوى للأخرين.

وهناك أيضاً مزرعة الدرن والتي تعتبر أكثر حساسية لتشخيص المرض، الا إنها تحتاج عدة أسابيع كي تعطي النتائج مما ينتج عنه تأخر في إعطاء العلاج للمرضى والمزيد من الإنتشار للمرض.

لذا كان من الضروري البحث عن طريقة دقيقة وسريعة لتشخيص الدرن الرئوي. ومن هنا جاءت هذه الدراسة لتقييم إحدى هذه الطرق وهي استخدام انزيم الادينوزين دى أمينيز لتشخيص الدرن الرئوي عن طريق قياس معدله فى الدم والغسيل الرئوى الناتج باستخدام المنظار الشعبى الضوئى الليفى.

وقد أجريت هذه الدراسة على خمسين شخصاً تم تقسيمهم إلى أربعة مجموعات :

المجموعة الأولى : عشرين مريض مصابون بالدرن الرئوى تم تشخيصهم بإيجابية البصاق للدرن عن طريق الفحص الميكروسكوبى المباشرلميكروب الدرن.

المجموعة الثانية : عشرة مرضى مصابين بسرطان الرئة تم تشخيصهم بفحص الأنسجة للعينات المأخوذة بالمظار الشعبى الليفى.

المجموعة الثالثة : عشرة مرضى مصابين بالإلتهاب الرئوى تم تشخيصهم اكلينيكيا ,وعن طريق الأشعة وسلبيى البصاق لميكروب الدرن.

المجموعة الرابعة : عشرة أشخاص غير مرضى.

جميع المرضى تم دخولهم قسم الامراض الصدرية بكلية الطب جامعة القاهرة ومستشفى صدرالجيزة بالعمرانية في الفترة من أكتوبر ٢٠٠٤ إلى مارس ٢٠٠٥ .

وقد أشارت الدراسة إلى ارتفاع معدل إنزيم الادينوزين دى أمينيز بشكل إحصائى ملحوظ فى الدم والغسيل الرئوى فى المجموعة الأولى التى تتكون من الأشخاص المصابين بدرن رئوى عن المجموعات الأخرى التى بها أشخاص مصابون بسرطان الرئة أو الإلتهاب الرئوى أو الأشخاص الغير مرضى.

لقد كان معدل الادينوزين دى أمينيز فى الدم (٢٥,٧ – ٩٧,٤) وحدة/ لتر فى الأشخاص المصابون بدرن رئوى و(٢١ – ٣٤,٢) وحدة / لتر بين مرضى سرطان الرئة من النوع الغددى و (١٤ – ٢٥,٣) وحدة/ لتر بين مرضى سرطان الرئة من النوع الخلوى و (١٢,١ – ٣٩) وحدة/ لترفى المرضى المصابون بإلتهاب رئوى و (١٢,١ – ٣٧,٤) وحدة/ لتربين الأشخاص الأصحاء .

وقد تم الحصول على النقطة القطع وهى ٢٦,٢، وكانت بنسبة الحسّاسية والتحديد ٩٥ %, ٨٣,٣% على التوالي بالقيمةِ التنبؤيةِ الإيجابيةِ ٧٩,٢ %.

و كان معدل الادينوزين دى أمينيز فى الغسيل الرئوى (٢,٧ – ٨,٣) وحدة/ لتر فى الأشخاص المصابون بدرن رئوى و(١,٣ – ٢,٤) وحدة / لتر بين مرضى سرطان الرئة من النوع الغددى و (١,٤ – ٥,٤) وحدة/ لتر بين مرضى سرطان الرئة من النوع الخلوى و (٠,٠ – ٣,١) وحدة/ لترفى المرضى المصابون بإلتهاب رئوى و (١,١ – ٢,٦) وحدة/ لتربين الأشخاص الأصحاء .

وقد تم الحصول على نقطة القطع وهى ٢,٥، وكانت بنسبة الحسّاسية والتحديد ١٠٠ %, ٨٣,٣ % على التوالي بالقيمةِ التنبؤيةِ الإيجابيةِ ٨٠ %.

وقد أشارت نتائج إلى أنه من الممكن استخدام قياس معدل الادينوزين دى امينيز فى الدم والغسيل الرئوى فى تشخيص الدرن الرئوى بشرط استبعاد بعض الامراض التى تؤدى الى ارتفاع الانزيم .

وقد أوصت هذه الدراسة بعدم استخدام قياس الانزيم كإجراء روتينى لتشخيص الدرن الرئوى لعدة أسباب :

- وجود كثير من الأمراض التى تؤدى الى ارتفاع معدله فى الدم.
- لإرتفاع تكلفته المادية فى مصر.

- استخدام الفحص الميكروسكوبى المباشر لميكروب الدرن فى البصاق كإجراء روتينى لتشخيص الدرن الرئوى فى معظم وحدات الأمراض الصدرية فى مصر.
- للحصول على الغسيل الرئوى يجب استخدام المنظار الشعبى الليفى وهو يحتاج إلى تقنية ومهارة خاصة وغير متوفر فى جميع وحدات الأمراض الصدرية فى مصر .