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**Phagocytosis of M. tuberculosis by a macrophage**

(Scanning Electron Micrograph Image Courtesy of Dr. Zahra Hasan)
EDITORIAL

In this issue, we present an Original study by Jamil, B. et al. this discusses the assessment of four mortality prediction models for patients in an ICU setting. Review articles discuss the very real dangers of transfusion transmitted malaria in an endemic setting and patterns of tuberculosis infections of the central nervous system. The review on of tuberculosis meningitis by Enam, A. et al. focuses on the diagnosis, clinical aspects and treatment of the disease. Pakistan has the eighth highest tuberculosis burden in the world. Extra-pulmonary forms of tuberculosis are an increased cause of disease due to problems in diagnosis of infectious such as, skeletal tissue, kidney, genitor-urinary tract and the brain. The causative agent of the disease is mycobacterium tuberculosis, which resides in the macrophage (the primary defense cell of the host). Our cover image reflects the uptake interaction between a mycobacteria and a macrophage host cell. In addition, improper screening of blood-by-blood banks has become an issue of national importance. The government has recently shut down a number of blood banks in the country. Efforts are being made to regularize blood-screening procedures. Moiz, B focuses on important considerations for blood screening.

Our case reports are becoming more interactive and readers are encouraged to write to us with their views, letters or news of developments in the field of infectious diseases.

This is the last issue for 2004 (OCT-DEC) and we will be formally applying for International indexing. The editorial board is reflecting change and we have invited leading international experts to come on board. The IDJP is the symbol of the Infectious Diseases Society of Pakistan and we look forward to raising our standards in the quest for international recognition.

This issue also leads up to the ISDP Annual National Conference; the 2nd National Conference on Infectious Diseases which will be held in Lahore 25-27 March, 2005. We look forward to seeing you in Lahore!

The Editors
Assessment of Four Mortality Prediction Models in Intensive Care Unit Patients with Sepsis

Bushra Jamil, Kiran Alam Qureshi, Maria Khan, and Veerta Ali Ujan.
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Abstract

Early recognition of sepsis and the rapid institution of therapy are absolutely essential for appropriate management of patients admitted to the hospital. Both score-generating clinical tools and clinical acumen are important for identifying the sick, while early intervention in acute deterioration is beneficial, before and after ICU admission. Several scoring systems have been devised which attempt to identify risk factors and predict outcome of different patient groups. The purpose of this pilot study was to assess the value of four mortality risk scoring systems, i.e. Mortality Probability Models (MPM) - admission, MPM - 24 hours, Simplified Acute Physiology Score (SAPS) II and Acute Physiology and Chronic Health Evaluation (APACHE) II, in predicting outcome in patients admitted to the intensive care unit with sepsis. The expected outcome was calculated according to the specifications of each system and was compared to the actual outcome.

Key words
Mortality risk prediction models, sepsis

Introduction

Infections are a leading cause of morbidity and mortality in Pakistan. Delay in diagnosis of serious infections and inappropriate or inadequate management lead to the development of systemic inflammatory response, followed by septic shock and death. Proper management of individual patients demands early recognition, accurate etiological diagnosis and appropriate treatment. In sepsis, the extent and involvement of different organ systems has been shown to affect outcome. This observation may allow the clinician at the bedside to recognize and respond early to adverse patterns and changes of organ system dysfunction in septic patients. Such an assessment can be facilitated and made more objective through the use of mortality prediction models. While several systems or models have been designed for intensive care unit (ICU) patients, there are some models which can be applied to non-ICU patients, who are not monitored invasively.

We conducted this pilot study to assess four mortality prediction models in our patients with sepsis. Various clinical and laboratory parameters were studied in patients admitted to the ICU with severe sepsis and septic shock. The outcome predicted by calculations defined in the models was compared with the actual outcome, in order to assess the reliability and utility of these systems in predicting outcome of sepsis.

Methods

Case records of 20 patients who were admitted to the ICU with the diagnosis of sepsis, over a period of 3 months in the year 2000, were studied retrospectively. Five patients had to be excluded because of insufficient data. The patients were selected randomly and based on the data available, were analyzed according to the following scoring systems: Mortality Probability Models (MPM) - admission, MPM - 24 hours, Simplified Acute Physiology Score (SAPS) II and Acute Physiology and Chronic Health Evaluation (APACHE) II. Inclusion criteria included age >18 year, signs and symptoms of local infection (cellulitis, septic arthritis, LRTI, UTI) or body temperature >38°C or < 36°C orally with one of the following: hypotension, defined as systolic blood pressure <90 mmHg or its reduction by >40 mmHg from patient’s baseline, in the absence of other causes for hypotension, tachycardia defined as a pulse rate >90 beats per minute, tachypnea defined as respiratory rate >20 breaths per min or PCO2 <32 torr, white blood cell count >12,000 cells/cumm or <4000 cells/cumm, or with a differential count showing >10% band neutrophil forms.

Exclusion criteria included age less than 18 years, admission due to extensive burns and coronary artery disease. Presence of significant coexisting illnesses was noted. The expected outcome was calculated on line at the official website of French Society of Anesthesia and Intensive Care (sfar.org), according to the specifications of each system. The predicted death rate was compared with the actual outcome of sepsis in each patient. Sensitivity, specificity and positive predictive value of each system were also determined.

Results

The study patients included 11 males and 5 females. Age ranged from 18 to 79 years with a mean of 52.1 years. Females were slightly older with a mean age of 57.4 years; mean age for males was 46.8 years. Most of the patients had more than one significant associated illnesses (table 1).
Diabetes mellitus was the commonest associated illness followed by renal failure and chronic liver disease. A significant number of patients had more than one co-morbid conditions concomitantly. Three patients did not have any underlying illnesses; one of them was 27 weeks pregnant. Infections of the skin and soft tissues, including cellulitis and necrotizing fasciitis were the commonest infections preceding sepsis and septic shock; pneumonia was also common (table 2). Ten patients expired (66.6%), 3 recovered from their illness and outcome of 2 patients who were transferred to another facility could not be ascertained.

Table 1. Significant coexisting illnesses in sepsis patients

<table>
<thead>
<tr>
<th>Co-morbid conditions</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>4 (26.2)</td>
</tr>
<tr>
<td>Hematological disorders&quot;</td>
<td>3 (20)</td>
</tr>
<tr>
<td>IHD/CMP</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Gut perforation</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>NHL</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Elephantiasis</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Mitral incompetence</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Liver abscess</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>1 (6.6)</td>
</tr>
</tbody>
</table>

"Acute lymphocytic leukemia (2) aplastic anemia (1)"  
"Ischemic heart disease/ cardiomyopathy"  
"Non-Hodgkin lymphoma"

Diabetes mellitus was the commonest associated illness followed by renal failure and chronic liver disease. A significant number of patients had more than one co-morbid conditions concomitantly. Three patients did not have any underlying illnesses; one of them was 27 weeks pregnant. Infections of the skin and soft tissues, including cellulitis and necrotizing fasciitis were the commonest infections preceding sepsis and septic shock; pneumonia was also common (table 2). Ten patients expired (66.6%), 3 recovered from their illness and outcome of 2 patients who were transferred to another facility could not be ascertained.

Table 2. Site of infection in patients with sepsis

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Skin and soft tissues</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Lung</td>
<td>4 (26.2)</td>
</tr>
<tr>
<td>Gut perforation</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (6.6)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1 (6.6)</td>
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</tbody>
</table>

The sensitivity and specificity of all the scoring systems were calculated and results are shown in table 3. The sensitivity of APACHE II for predicting mortality was 100% at the score of >22 which translates into a predicted death rate of >42.4. For the rest of the scoring systems, sensitivity ranged from 77 to 87%. Specificity was highest at 55.5% for SAPS II.

Table 3. Sensitivity, specificity and positive predictive value of mortality prediction models

<table>
<thead>
<tr>
<th>Scoring system</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II</td>
<td>100 at score of &gt;22</td>
<td>45.4</td>
<td>0.45</td>
</tr>
<tr>
<td>SAPS II</td>
<td>87.5 at score of &gt;39</td>
<td>55.5</td>
<td>0.636</td>
</tr>
<tr>
<td>MPM admission</td>
<td>80 at score of &gt;20</td>
<td>50</td>
<td>0.727</td>
</tr>
<tr>
<td>MPM 24 h</td>
<td>77.7 at score of &gt;19.4</td>
<td>42.8</td>
<td>0.636</td>
</tr>
</tbody>
</table>

*positive predictive value

Discussion

Severe sepsis and septic shock are major reasons for hospital and intensive care unit admissions. Data from the Aga Khan University Hospital shows that over the last 15 years, the overall mortality due to sepsis has remained around 36.6%. Mortality rate in patients with septic shock has been a staggering 81%. This is excessive in comparison mortality rates ranging from 40-60% quoted in literature. In critically ill patients in the intensive care unit (ICU) who are already compromised because of coexisting serious co-morbidities, septic shock may be associated with higher mortality. It has been shown that the systemic inflammatory response to severe infection evolves in stages from sepsis to severe sepsis to septic shock with corresponding increases in the proportion of patients with positive blood cultures, end organ failure and crude mortality. It is logical to presume that the progression of sepsis and 28-day mortality may be influenced by effective early interventions. Even those patients who have developed end organ damage and shock might benefit from early identification and rapid support. Studies have shown that the crude mortality of all patients in an intensive care as well as that for patients with septic shock in an ICU decreases if physicians remain in the hospital and are supervised by subspecialists trained in critical care. The ability of the highly skilled ICU personnel and the ability of the sophisticated patient monitors would be expected to have detected the onset of shock at an earlier point in time. Additionally, the ICU has highly skilled physicians, nurses and support personnel who have the ability to evaluate patients more frequently with continuous assessment of vital signs. The typical ICU patient is monitored with sophisticated equipment which is expected to alert the ICU staff to critical alterations in the patient’s clinical status. The result would be earlier detection and treatment of septic shock. In contrast, general ward patients do not have access to the same frequency or intensity of assessments and monitors, resulting in delays in the detection of shock onset. The prolonged period of hypoperfusion of critical organ beds, such as liver, brain, heart, kidney and gastrointestinal tract may give rise to multiple organ dysfunction and failure, which is associated with a high rate of morbidity and mortality.
In septic patients, the number of organ systems with impaired function is important because it correlates with clinical outcome\textsuperscript{9,10,11}. It has been shown that the pattern and evolution of organ system dysfunction over the first 3 days of sepsis is significantly related to 30-day mortality\textsuperscript{12}. This observation may potentially allow the clinician at the bedside to recognize and respond early to adverse patterns and changes of organ system dysfunction in septic patients. Clinical assessment can be facilitated and made even more objective through the use of mortality prediction models. While such systems have been designed for ICU patients, some of these can easily be applied to non-ICU patients, who are not monitored invasively.

However, debate still continues about the accuracy of these scoring systems, their efficiency in assessing the severity of illness and whether they have a prognostic role in the estimation of the illness outcome. Additionally, these tools have to be validated in the population in question before they are adopted for outcome prediction and decision making.

We studied Mortality Probability Models (MPM) - admission, MPM - 24 hours, Simplified Acute Physiology Score (SAPS) II and Acute Physiology and Chronic Health Evaluation (APACHE) II to assess their utility in predicting mortality in our patients.

It has been emphasized that the calculation of a risk assigned to a measured score is an epidemiologic tool, and should not be used as a single patient prevision tool. However, sequential calculations may be of immense importance in early recognition of deterioration and the need for more aggressive intervention in patients who present at an early stage of sepsis. Through early diagnosis and intervention, we may be able to decrease mortality associated with sepsis and septic shock in our patient population.

In the current study, we recruited ICU patients only because of variables in APACHE II system. MPM - admission, MPM - 24 hours and SAPS II could be used in non-ICU patients as well. Most of the patients in our study had serious concomitant illnesses, which could have contributed to mortality. While APACHE II correctly predicted mortality above a certain score, and proved to be the most sensitive of the models studied, SAPS II was the most specific system for this purpose. The other systems too performed reasonably well, although calculations on sensitivity, specificity and positive predictive value may not be entirely reliable with a small sample size.

There is a need to study the utility of these models in early recognition of sepsis-related complications in a large cohort of our patient population, before recommending them as essential tools for bedside evaluation of patients with sepsis.

References

1. Bone RC. Gram negative sepsis: Background, clinical features, and intervention. Chest 1991;100:802-808
Prevention of Transfusion Transmitted Malaria in an Endemic area– A Challenge for Blood Banks

Dr. Bushra Moiz
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Background:

Malaria is one of several blood borne infections that are transmitted through transfusion of blood. The disease is caused by Plasmodia, of which two species vivax and falciparum are prevalent in Pakistan. Transmission of this parasite through blood transfusion is important as only a small number of infected red cells from donor can lead to malaria in the recipient. Moreover, the diagnosis is often missed and unexpected in a patient who is otherwise critically sick. This may be life threatening in extreme cases, especially if the species is Plasmodium falciparum.

The first case of transfusion malaria was reported in 1911. Since then increasing number of cases have been reported world wide. The risk of acquiring malaria through transfusion is dependent on incidence and prevalence of the disease at a particular area. In countries like USA and Canada, where malaria is not endemic the incidence is as very low. The annual incidence reported by US Center for Disease Control (CDC) is only 1 -3 cases per year. However, in endemic countries like ours, the rate of transmission may be as high as 50 cases per million blood donation. We do not know the actual prevalence of transfusion transmitted malaria in Pakistan. The incidence was reported to be nil by Rahman M et al in 2003 from Punjab. However, this appears to be an underestimation of overall burden of transfusion malaria that can be measured only through a comprehensive national surveillance program.

In a country like ours where malaria is endemic, there is a need of screening every donor through proper laboratory tests to alleviate the chances of post transfusion malaria.

Laboratory screening for Transfusion-transmitted Malaria

National Institute of Health (NIH) consensus conference in 1995 requires that every donor blood should be screened for various infections including HIV, Hepatitis B and C, malaria and syphilis. However, there is no suitable test yet available for screening malaria in the donors. The different diagnostic tests available for malaria include examination of peripheral smear, QBC, various serological tests including PCR. However, all of these tests have their limitations in terms of specificity, sensitivity and cost-effectiveness. Hence, it the challenge for a blood bank to properly screen the donated blood for malaria by a test which should be simple, sensitive, fast and at the same time economically feasible also.

Various strategies for Screening Malaria:

1. Donor history: A report prepared by WHO in 1998 stated that the most effective way of screening donors is to take proper history of malaria or fever that could be due to malaria. Donor selection criteria should be designed to exclude potentially infectious individuals from donating red cells. However, the infected donor may have a very low parasitemia; he may not have a clinical history of recent past or present history of febrile illness. Thus, there are good chances that he may pass out through donor screening process. Further more, the acquired immunity in adults in malaria endemic areas may result in low grade parasitemia without symptoms. Such carriers can also be difficult to identify on history basis alone.

Federal Drug Administration (FDA) and American Association of Blood Bank (AABB) had set the following criteria for donors who have traveled to or lived in an endemic area:

1. Travelers may donate blood 6 months after returning from endemic areas provided they are free of symptoms and have not taken anti-malarial drugs.
2. Persons with past history of malaria should be deferred for 3 years after becoming asymptomatic.
3. People who had been on chemoprophylaxis can donate blood after 3 years of stopping their therapy.
4. Immigrants or visitors from endemic area can be accepted as donors 3 years after departure if they are asymptomatic.
5. Proven carriers of malaria or persons who had malaria due to P malariae are excluded permanently from donating blood.

The 3 years limit has been established because infection with the relapsing forms of malaria (Plasmodium vivax and Plasmodium ovale) rarely persist for more than 3 years after a naturally acquired infection. Infection with Plasmodium falciparum usually has clinical malaria with in 3 months but may show asymptomatic infection for a year or more. Plasmodium malariae may remain undetected in blood for several years.

However, these deferral policies are not practical for endemic areas as exclusion would include nearly all the donors.
Furthermore, it is not always possible to obtain accurate travel and immigration history. Some cases of transfusion transmitted malaria would always occur because of occasional asymptomatic persistence of malarial parasites.

2. Examination of Peripheral film:

The gold standard for malaria diagnosis is peripheral film examination. However, this is very labor intensive and skill effective. The reason is that the asymptomatic blood donors have very low levels of parasite count and sensitivity of peripheral film microscopy declines in parallel with the density of malarial parasites in the blood. Thus, microscopy of blood films involving a large numbers of blood donors on daily basis seem to be impractical.

3. QBC:

It is another method of identifying the malarial parasites in the peripheral blood. It involves staining of the centrifuged and compressed layer of red cell layer with acridine orange and its examination under UV light source. It is fast and more sensitive than smear examination and can detect parasites even less than 100/ul. However the test is non specific and stains nucleic acid from all cell types and therefore technically demanding. The major disadvantage is that it requires costly equipment and consumables.

4. Automated analyzers:

Some hematology cell counters detect parasites by giving abnormal signals that are produced by hemozoin in white cells. Hemozoin is the pigment produced by the parasites as a breakdown product of hemoglobin present in host red cells. As the red cells rupture, they release hemozoin which is engulfed by phagocytic cells like neutrophils and monocytes. Initial studies have shown good results in terms of sensitivity and specificity. But its value in donor screening is yet to be evaluated as parasitemia and production of hemozoin is lower in them.

5. Rapid diagnostic tests:

Immunochromatographic tests are based on the detection of parasite antigens from the peripheral blood using either monoclonal or polyclonal antibodies against the parasite antigen targets. Currently these tests capture histidine rich protein II, a pan malaria aldolase and parasite specific lactate dehydrogenase. The rapid diagnostic tests are simple, user friendly not requiring skilled technologists and equipment. These tests usually have a sensitivity of 35-97% for P falciparum and 2-97% for P vivax or non-falciparum species. There is also a possibility of false positive and false negative results with these tests. The sensitivity of these tests is considerably less at low levels of parasitemia and non immune individuals.

These assays may serve as a promising test for screening our donors. But there is a need to develop the devices so that they may have high acceptable sensitivity and an affordable cost.

6. ELISA:

It is an interesting alternative for the screening of blood donors. It is automated with fast through put and compatible with other transfusion screening procedures. However, the test lacks sensitivity as the low levels of antibodies cannot be detected by this method. A study done recently demonstrated that combined detection of antigens and antibodies may represent a sensitive strategy for the testing of blood donors. More trials are required before ELISA can be accepted as a valuable option for this purpose.

7. PCR:

The major advantages of using a PCR based technique are its high sensitivity as it can detect parasites as low as 5 or less per µl of blood and identification of species. Rubio et al in 1999 found semi nested PCR to be very useful for screening donors at risk who were immigrants in Spain. However, the test may be positive after successful treatment of malaria as PCR can detect DNA from non viable parasites also. Hence, PCR testing in endemic areas will result in false positive results with too much loss of donated blood. The other associated problems are its prolonged time frame and cost ineffectiveness. The cost of screening through PCR was estimated to be $3,972,624 per case of malaria averted.

Although PCR technique is very promising for the screening of malaria, but still it can not be considered as a method of choice for our purpose. The future advances in PCR technique may help to overcome the problems of cost and timings.

Conclusions:

Transfusion associated malaria is often severe and fatal. The detection of infected donor is difficult in endemic areas due to the lack of suitable screening test. Deferral of donors based on history is not practical for endemic areas. Blood smear staining techniques show poor results due to the low parasite concentration in many asymptomatic blood donors. Antibody detection test is not helpful because of universal presence of the antibodies in healthy donors in malaria endemic areas. Malarial antigen test seem to be promising but more costly. PCR technique, although is the most sensitive test is not economically feasible and impractical also because of its prolonged duration.
It is highly amenable that sensitive tests which are simple, fast, cost effective should be introduced for malaria screening in blood donors.

References:

Patterns of Tuberculosis in the Central Nervous System

Soobia Raza¹, Aliyah Sadaf¹, Faisal Fecto¹, Rushna Pervez Ali¹, Ehsan Bari¹, S. Ather Enam²
The Aga Khan University Medical College¹, Section of Neurosurgery², Aga Khan University Hospital, Karachi.

Introduction

Tuberculous involvement of central nervous system (CNS), although not very frequent, results in severe morbidity. Tuberculosis (TB) is endemic in developing countries but even in developed countries, after an initial decline up until 1980's, incidence of TB is on the rise. The AIDS epidemic, emergence of multi-drug resistant strains and immigration of people from endemic areas are some of the factors significantly contributing to this increase. Consequently, the burden of central nervous system tuberculosis has increased significantly worldwide.

Infection of CNS by tuberculosis (TB) can develop in several patterns. The old adage “Syphilis - the Great Masquerader”, probably applies to tuberculosis as well when it involves the central nervous system. This poses a constant challenge to the clinicians in making a definitive diagnosis. The various extra-pulmonary manifestations of tuberculosis and the multitude of organs involved complicate the task further. Central nervous system (CNS) tuberculosis forms a significant proportion of extra-pulmonary tuberculosis¹. In most cases, infection is thought to spread hematogenously. Due to a lack of reliable diagnostic tests and due to morbidity inherent in surgical procedures for diagnosis, the decision to treat central nervous system tuberculosis is done empirically in most endemic areas. Thus its purulent to be cognizant of the patterns of CNS infection by TB.

There are four major patterns of CNS TB:

1- tuberculous meningitis (TBM)
2- tuberculomas in brain and spinal cord (TBT)
3- tubercular brain abscess (TBA)
4- tuberculous encephalopathy (TBE)

Tuberculous Meningitis

The most common form that tuberculosis takes in the central nervous system is TBM. This is characterized by accumulation in the meninges of gelatinous exudates commonly affecting the cranial nerves. This exudate is composed of mononuclear cells, epithelioid cells and Langhans' giant cells. It usually arises from subependymal regions from small caseous foci known as “Rich” foci (Greenfield). Copious exudates of TBM may cause obstruction in CSF flow at the level of basal cisterns (basal arachnoiditis) resulting in communicating hydrocephalus (Figure 1). An incidence of hydrocephalus as high as 80% in tuberculous meningitis has been reported. Accumulation of exudates in the basal regions may compress optic chiasm, nerves and internal carotid arteries. Opto-chiasmatic arachnoiditis can lead to blindness in 5-10% of cases with TBM. Patients with tuberculous meningitis are clinically staged according to their presenting symptoms and their stage at diagnosis correlates directly with individual prognosis (Table 1).

Figure 1. MR image in a case of tuberculous meningitis. Coronal cut showing enhancement of the meninges in the left Sylvian fissure (a) and basal meninges (a,b). Resultant hydrocephalus is also evident in the MR images particularly in (b)
In many developing countries tuberculous meningitis is especially common in patients younger than 5 years. Infants usually present with non-specific symptoms, which include irritability, restlessness poor feeding, and physical signs of hydrocephalus. In immunocompromised patients, tuberculous meningitis manifests clinically in a similar manner. That TBM complicates a significant number of TB in developing countries and that TBM incidence is increasing progressively compared to other extra-pulmonary TB even in developed countries is shown in Figure 2.

Two other conditions that need to be considered with TBM are tuberculous vasculitis and tuberculous encephalitis. The exudative inflammatory change in the meninges may extend along the perforating vessels and incite reactive proliferation of microvessels. This extension can give rise to encephalitis which may or may not be focal. Vasculitis may cause thrombosis in the perforating and other small vessels and occasionally in larger vessels such as middle cerebral artery leading to ischemic changes and multiple infarcts, one of the main perilous outcomes of TBM.

### Tuberculomas

A tuberculoma is an infrequent manifestation of central nervous system tuberculosis. It may occur singly but is more often multiple. In approximately 16% of patients, it may co-exist with culture positive tuberculous meningitis. At Aga Khan University Hospital (AKUH), Karachi, Pakistan 246 patients were admitted during the period of 2000-2004 with the suspicion of tuberculous meningitis. 89 (36.1%) of these had tuberculomas, either with or without culture positive tuberculous meningitis (unpublished observations). The most common site for TBT is posterior cranial fossa (Figure 3).
The reason for this is not well understood but might be the predilection of TBM to occur in basal regions which eventually gives rise to TBT. Posterior fossa location of TBT is particularly more common in patients less than 20 years. Compression of the CSF pathway either in the 4\textsuperscript{th} ventricle or at the cerebral aqueduct by tuberculomas gives rise to hydrocephalus. Microscopically, it is composed of a caseous center surrounded by a granulomatous reaction including giant cells, lymphocytes and fibrosis. Unusual presentations of TBT may consist of multiple small perivascular “incipient type” granulomas which develop as gradual conglomeration on cortical surface, miiliary neuro-tuberculosis, cystic tuberculomas, and tuberculomas in subdural or trans-dural locations\textsuperscript{6}. Tuberculomas were one of the most common space occupying lesions in the beginning of the twentieth century. Their incidence dropped to less than 2\% during the latter half of the same century in developed countries but it continues to constitute a significant proportion of intracranial mass lesions in developing countries (8-12\%)\textsuperscript{7}. The clinical features of intracranial tuberculomas are related to the mass effect, local or general, produced by the lesion (Table 2).

**Tuberculomas in the spinal cord may present with signs and symptoms of myelopathy spinal cord compression, or rarely radiculopathy\textsuperscript{4}.**

**Tubercular Brain Abscess**

TBA is a rare form of central nervous system tuberculosis. It is characterized by an encapsulated collection of pus, containing viable tubercular bacilli with or without evidence of tubercular granuloma\textsuperscript{8}. Not more than 25 cases have been reported so far in literature. They are typically larger than tuberculomas and evolve rapidly. The exact mechanism of their formation is unknown. Occasionally tuberculomas may contain super-infection by other bacteria\textsuperscript{10}. The signs and symptoms due to TBA may not be much different than those from TBT except for its fast progression (Table 3).

**Table 3**

Predictors of Poor Prognosis in CNS TB (Ref. 29-33)

<table>
<thead>
<tr>
<th>Predictor</th>
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<tbody>
<tr>
<td>Clinical condition</td>
</tr>
<tr>
<td>• Decreased mental status</td>
</tr>
<tr>
<td>• Focal neurological deficits</td>
</tr>
<tr>
<td>• Cranial nerve palsies</td>
</tr>
<tr>
<td>• Convulsions</td>
</tr>
<tr>
<td>• Mechanical ventilation</td>
</tr>
<tr>
<td>Coexisting miliary or extrameningeal tuberculosis/ coinfection with HIV</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>• Very young</td>
</tr>
<tr>
<td>• Age greater than 60 years</td>
</tr>
<tr>
<td>CSF values</td>
</tr>
<tr>
<td>• Culture positive for MTB</td>
</tr>
<tr>
<td>• Raised protein</td>
</tr>
<tr>
<td>• Reduced glucose</td>
</tr>
<tr>
<td>Delayed or interrupted treatment</td>
</tr>
</tbody>
</table>

**Tuberculous Encephalopathy**

TBE is another rare outcome of TB invading CNS. It is usually more common in younger population and is characterized by diffuse brain edema and demyelination which usually is extensive\textsuperscript{11}. Microscopically it is characterized by microvascular necrosis with perivascular macrophage reaction and demyelination along with focal glial nodules in the white matter and occasional hemorrhagic lesions. Combination of progressive tuberculosis along with severe alcoholic intoxication has been characterized as acute toxic encephalopathy syndrome\textsuperscript{12}. This syndrome is characterized by impaired consciousness, epileptic seizures, disseminated intravascular coagulation, signs and symptoms of meningitis without spinal fluid changes. This syndrome may be one of the leading causes of neurologic devastation and death in CNS TB patients with high alcohol intake.

Spinal tuberculosis (Pott’s disease), the most common form of skeletal tuberculosis will be mentioned here briefly as it frequently leads to neurologic deficits. It may result in serious consequences like deformity and paraplegia due to bony destruction. TB spine may also lead to epidural tuberculous abscess or less commonly subdural tuberculous abscess. An increased predominance of spinal TB in immunocompromised individuals has been noted. Chemotherapy is the mainstay of treatment, with surgical procedures reserved for cases which are medically untreatable.

**Diagnosis**

Both TBT and TBA remain difficult to diagnose and rapid-turn around testing with high predictive values is needed. Clinical features supported by indirect evidence such as CSF examination and imaging studies of the head and spine have been used for early diagnosis. The differentials to be considered
in tuberculous meningitis are other bacterial meningitides, fungal infections, central nervous system toxoplasmosis and central nervous system lymphoma. The differential diagnosis of tuberculoma should include sarcoid granuloma, primary brain tumors, pyogenic abscess, fungal infections, cystic astrocytoma, lymphoma, cysticercosis and metastatic lesions. The differential diagnosis in AIDS patients must include opportunistic infections such as toxoplasmosis.

**Laboratory Methods**

Conventional bacteriological methods rarely detect Mycobacterium tuberculosis in cerebrospinal fluid (CSF) and are of limited use in the diagnosis of TBM. CSF protein between 100-200 mg/dl, CSF glucose less than 40 mg/dl, CSF leukocyte count between 50-500/microl with predominant CSF lymphocytes are considered characteristic findings in TBM patients. Tuberculous meningitis could be confirmed in half of clinically suspected cases by this method.

Polymerase Chain Reaction (PCR) offers a rapid and fairly accurate diagnosis of tuberculous meningitis. Although specificity and sensitivity as high as 100% have been reported, until there is advancement in PCR technique, this test alone is insufficient as a single diagnostic test for tuberculosis. Furthermore, in recent studies, immunological diagnostic techniques were found to be superior to PCR. These methods, owing to their rapid yield and easier method, also seem convenient for use in laboratories in the developing world. Gene probes, gene amplification methods and in situ approaches offer unparalleled capability to enhance the diagnosis of tuberculosis in the near future.

**Radiological Evaluation**

Modern imaging is a cornerstone in the early diagnosis of central nervous system tuberculosis and may prevent unnecessary morbidity and mortality.

**Chest X-ray:**

The chest x-ray in patients with central nervous system tuberculosis may show features of miliary or pulmonary tuberculosis. In about 47% of central nervous system tuberculosis patients, the CXR may not reveal any abnormalities.

**Computerized Tomography (CT):**

In patients with tuberculous meningitis, hydrocephalus is the most common (80%) abnormality detected by CT. Less commonly; parenchymal/basal cistern enhancement is noted. Cerebral infarcts and surrounding edema can be detected in approximately 13% of patients, while tuberculomas can be detected in up to 5% of patients with tuberculous meningitis. The CT can be normal in up to 12% of patients.

In patients with tuberculomas, the characteristic CT finding is a nodular enhancing lesion with a central hypodense region. Such a lesion arising due to tuberculous involvement of the central nervous system is difficult to differentiate on CT from other intracranial diseases i.e. abscesses, neoplasms, multiple sclerosis, gliosis etc. Extensive surrounding edema and mass effects are usually seen in the acute inflammatory stage but are not as prominent in chronic tuberculomas. The appearance of TBA on CT is similar to tuberculomas and to that of other intracranial abscesses, showing lesions with central hypodensity and peripheral enhancement.

**Magnetic Resonance Imaging (MRI):**

Contrast enhanced MRI is generally considered as the modality of choice for detecting and assessing central nervous system involvement by tuberculosis. The MRI may demonstrate localized lesions and meningeal enhancement. It is useful for assessment of the location of lesions and their margins, as well as ventriculitis, menigitis and spinal involvement (sensitivity 86%, specificity 90%). Choroid plexus enhancement with ventricular enlargement on MRI is highly suggestive of TBM. In TBM, MRI shows diffuse, thick, meningeal enhancement. Cerebral infarcts can be seen in nearly 30% of cases. While current radiological methods such as CT and MRI are able to identify abnormalities highly suggestive and in some cases diagnostic of TBM, their overall diagnostic yield is less than optimal.

The MRI features of the individual tuberculoma depend on whether the granuloma is non-caseating, caseating with a solid center, or caseating with a liquid center. The non-caseating granuloma usually is hypointense relative to brain on T1-W images and hyperintense on T2-Weighted (T2-W) images and, shows homogenous post-contrast enhancement. The caseating granuloma with solid caseation appears relatively hypointense or isointense on T1-W images and isointense to hypointense on T2-W images. The granulomas with central liquefaction of the caseous material appear centrally hypointense on T1-W image and hyperintense on T2-W images with a peripheral hypointense rim on T2-W images. Gadolinium enhanced T1-W images show rim enhancement in caseating granulomas.

**Role of Biopsy**

Establishing a diagnosis of TBT can be very challenging as the TBT lesions are similar to myriad of other lesions on imaging studies. Accurate diagnosis of tuberculoma is not possible until the brain lesion in question is subjected to histopathological examination. Seven out of 13 patients, who underwent biopsy at AKUH for suspicion of tuberculoma, had other diagnoses (unpublished observations). Although surgical intervention is considered mandatory in clinically diagnosed tuberculoma patients with worsening clinical or radiological features, definite guidelines regarding surgical biopsy for diagnosis are lacking.
Treatment and Prognosis

Anti-tubercular therapy (ATT) is the mainstay of management in central nervous system tuberculosis. Meta-analysis and RCT have suggested that corticosteroids are beneficial in the survival of patients with CNS TB\(^{25,26}\). The duration of ATT may need to be adjusted to radiological response when treating tuberculomas\(^9\). Despite ATT, mortality is reported to be high in tubercular abscesses\(^9\).

Surgery has a role both in the diagnosis and treatment of tuberculosis. It is usually indicated in cases of clinical deterioration that fail to respond to medical management and when the diagnosis of tuberculosis is in doubt. Surgical treatment options for TBA include simple puncture, continuous drainage, fractional drainage, repeated aspiration through a burr hole, stereotactic aspiration and total excision of the abscess. Ventriculoperitoneal shunts may be required in patients with TBM or TBT who develop obstructive hydrocephalus. Ventriculoperitoneal shunt should be performed at the time the need for shunting is determined and should not be delayed waiting for the infection to resolve\(^20\).

Despite prompt initiation of effective ATT, central nervous system tuberculosis continues to have a poor prognosis. Complications of tuberculous meningitis constitute the major causes of morbidity and mortality of central nervous system tuberculosis, especially in the pediatric population.

Patients with stage 1 disease at presentation usually make a complete recovery or are left with only mild neurological deficits, while around 30% of patients with advanced stage at presentation succumb to severe residual neurological sequelae\(^8\). Those who survive central nervous system tuberculosis are left with serious dysfunctions such as cognitive disturbances, seizures, hemiparesis, ataxia, visual impairment, optic atrophy and other persistent cranial nerve palsies. Children and older persons, because of their less competent immune systems are more vulnerable to contracting central nervous system tuberculosis. In a recent study, approximately 28% of paediatric patients with central nervous system tuberculosis died and 40% were left with permanent severe neurological sequelae\(^8\). Some of the predictors of poor prognosis in patients with central nervous system tuberculosis are shown in table 3. It is likely that BCG protects against a fatal outcome in tuberculous meningitis\(^8\).

Conclusion

Central nervous system tuberculosis is one of the more severe forms of extra-pulmonary tuberculosis. There has been a significant increase in the incidence of CNS TB worldwide over the last couple of decades.

It may present as tuberculous meningitis, tuberculoma, tuberculous abscess, or encephalopathy. Its diagnosis relies on laboratory studies of the CSF and/or visualization of a lesion on CT or MRI. Newer diagnostic techniques, such as PCR, have not been assessed completely and are not possible in most settings in the developing world. Neurosurgeons have been actively involved in the treatment of central nervous system tuberculosis due to its propensity to cause obstructive hydrocephalus, intracranial mass lesions, and compressive myelopathy. Surgery has a role both in the diagnosis and/or treatment of tuberculoma and tubercular brain abscess although definite guidelines have yet to be formulated. A high index of suspicion is required in order to avoid delays in diagnosis, which may influence treatment outcome. Death may occur as a result of missed diagnosis and delayed treatment.

References

SUMO Vs Viruses
What’s the Connection?

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Some proteins are synthesized inactive and need to be post-translationally modified to become active. These various types of modifications are phosphorylation (addition of PO4), acetylation (CH3CO), methylation (CH3), and ubiquitination (Ub). One type of modification that has been receiving a lot of attention lately is the addition of a 97 AA peptide, called SUMO (for small ubiquitin-like modifier), to a number of proteins.

It is well known that proteins that are targeted for degradation are modified by ubiquitin, a 76 amino acid peptide. This is carried out by the E1, E2 and E3 ubiquitin activating, conjugating and ligating enzymes, respectively. Although there is only one type of E1, four different types of E2 and over 100 different types of E3 are found in humans; overall there are over 300 different combinations of the E2-E3 enzymes each of which specifically target different sets of proteins. Once modified, the mono or poly-ubiquitinated proteins are subsequently degraded by the 26S proteosome, which represents 1% of the total protein inside a eukaryotic cell, into small peptides. Thus ubiquitination is an irreversible modification (no de-ubiquitinases have been found!) whose primary function is to degrade proteins.

Like ubiquitin, SUMO modification also takes place on the terminal amino group of lysines. Moreover, there are E1, E2 and E3 SUMO ligases whose respective functions mirror that of the ubiquitin modifying enzymes. SUMOylation is a reversible process that is catalyzed by de-conjugation proteases Ulp/Senp. Other homologs of SUMO, namely SUMO-2 and SUMO-3 have also been found recently and even though SUMO2 and SUMO3 share 50% amino acid sequence identity with SUMO1, both are functionally different.

The main difference between the two is that SUMOylation can modify the function, activity, or localization of its various target proteins. Although the biological roles of SUMO modification remain poorly understood, recent reports suggest that SUMOylation plays an important role in protein stability, DNA repair, gene regulation, protein transport, and chromosomal segregation. Additionally, SUMOylation has been shown to play an active role in neurodegenerative diseases such as Huntington’s and Alzheimers. For instance, it has been shown recently that the Huntingtin protein (Htt) becomes more neurotoxic after it has been SUMOylated.

A number of recent reports have also demonstrated that SUMOylation can enhance the infectivity by certain viruses. Human cytomegalovirus (HCMV) is a member of the herpesvirus family and while HCMV poses a low threat to healthy individuals, it is life threatening to the immuno-compromised patients. HCMV infection requires the expression of IE1 (72 kDa) protein. Interestingly, SUMO1 modification of IE1 increases HCMV replication by promoting accumulation of IE2 (86 kDa) protein. Inhibition of sumoylation therefore would prevent infection by HCMV. This demonstrates that SUMO might be a good target for therapeutic intervention against HCMV infection.

New therapies are eagerly sought after to find the possible treatment of HIV. HIV-1 expresses several regulatory proteins that divert key cellular factors to allow rapid and efficient production of viral particles. Research for small peptides to penetrate and bind to the target protein has found two regulatory proteins; Tat and Rev. Tat and Rev are small proteins that act through protein-protein interactions, which is absolutely necessary to viral replication. Both Tat and Rev are stabilized by SUMO-1 modification which led to the formation of small protein, SUMO-1 heptapeptide transduction domain SHP, that can efficiently penetrate within primary lymphocytes and inhibit the function of Rev. These proteins have also been shown to inhibit viral replication in both lymphocytes and macrophages. Thus sumoylated small proteins might represent new therapeutic agents useful for impairing generation of new viral particles.

Other targets of SUMO addition include DNA repair and genome stability proteins, stress related proteins, DAXX, and transcription factors. The transcriptional activation of p53, called the “guardian of the genome” is increased by SUMO addition. Sumoylation may also alter the stability of proteins with polyglutamine repeats involved in neurodegenerative disorders, adding further and diverse roles of this modification system.
A Young Man with Fever and Abdominal Pain.

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20 year old young man presented to a general physician with complaints of high grade fever (103-104°F) for last five days with right sided abdominal pain without any nausea, vomiting or cough. On examination he was unable to take a deep breath because of pain, there was no positive finding on the rest of the abdominal exam.

What should be the next step?
- Ultrasound abdomen
- Broad spectrum antibiotics
- CXR
- Abdominal X Ray
- Urine D/R.

Although the patient had symptoms suggestive of intrabdominal pathology we have to remember that causes above the diaphragm can also lead to abdominal pain. This patient had abdominal ultrasound performed which demonstrated moderate right sided pleural effusion and the rest of the exam was normal.

At this stage what should be the next most appropriate step.
- Diagnostic Pleurocentesis
- Therapeutic pleurocentesis
- Antibiotics to cover for community acquired pneumonia
- CBC and ESR
- Pleural biopsy

Patient was started on broad spectrum antibiotics after CBC and diagnostic pleurocentesis performed as an out patient. He was also started on adequate analgesia to control the pleuritic chest pain.

The results of CBC demonstrated:
- Hemoglobin 14Gm/L
- TIC 6500mm³
- Neutro 47%
- Lympho 48%
- Platelets normal

The pleural fluid analysis demonstrated:
- Protein 5 Gm/L
- LDH 450 IU

At follow up visit after two days; he was still febrile but feeling a little better with adequate pain relief.

At this point in the course of his illness what is the most appropriate next step.
- Hospitalize the patient and start I/v antibiotics
- Change the antibiotics and continue out patient treatment
- Repeat the pleurocentesis to rule out complicated para pneumonic effusion /empyema
- Pleural biopsy to rule out acute tuberculous pleuritis
- Continue with present antibiotic as it is too early to see the response.

At this stage of patient’s illness, although with exudative effusion and high grade fever, acute community acquired pneumonia with parapneuomonic effusion is the most plausible diagnosis but a few things are atypical for this presentation.

He presented with symptoms suggestive of pleuritis without any cough, sputum production antecedent to the pain. With high grade fever and moderate exudative effusion his TLC count is not elevated also the chest X-ray does not demonstrate any underlying consolidation so alternate diagnosis must be considered, including acute tuberculous pleuritis.

Patient underwent pleural biopsy while initial antibiotics were continued.

Pleural biopsy demonstrated caseous necrosis. AFB smear was negative and PCR for mycobacterium Tuberculosis was positive. Diagnosis of acute tuberculous pleuritis was made and he was started on standard four drug anti-tuberculous treatment.

Discussion:

Diagnosis of tuberculous pleuritis should be kept in mind in any patient with an exudative pleural effusion. When a tuberculous effusion results in the absence of radiologically apparent tuberculosis it may be the continuation of primary infection 6 to 12 weeks formerly or it may represent reactivation tuberculosis. The tuberculous pleural effusion is believed to
result from disruption of sub pleural caseous foci into the pleural space. It leads to the entry of the tuberculous proteins into the pleural space generating a hypersensitivity reaction. Although tuberculous pleuritis and pleural effusion are generally considered a chronic illness; tuberculous pleuritis is usually an acute febrile illness causing a nonproductive cough and pleuritic chest pain mimicking acute bacterial pneumonia, but without an elevation in the peripheral white blood cell (WBC) count. If both cough and chest pains are present, pain usually antedates the cough. Night sweats, chills, weakness, dyspnea, and weight loss can also occur. In one series one quarter of the patients had initial symptoms of less than a week in duration, where as almost three quarter had symptoms for almost a month. Sometimes the onset is less acute with only mild chest pain, perhaps with non productive cough, a low grade fever, easy fatigability and weight loss. Pleural effusion due to tuberculous pleuritis is usually unilateral and can be of any size. In about 20% of patients with tuberculous effusion parenchymal diseases is radiologically visible almost always on the same side of the effusion and invariably represents an active parenchymal disease.

Diagnosis:

The identification of tuberculous pleural effusion depends upon the display of tubercle bacilli in the sputum, pleural fluid, or pleural biopsy specimen, or the expression of granulomas in the pleura. The primary diagnostic tests in tuberculous pleuritis involve sampling of the pleural fluid and pleural tissue. Pleural fluid mycobacterial smears are generally negative, unless the patient has tuberculous empyema. Pleural fluid culture is positive for M. tuberculosis in fewer than 40 percent of patients; a BACTEC system with bedside inoculation provides a higher yield than do conventional methods. Pleural biopsy culture is positive in 64 percent. Pleural tissue can be obtained via thoracoscopy or closed percutaneous needle biopsy. The two methods are believed to have comparable sensitivities, and the latter is generally preferred because it does not require general anesthesia. Sputum culture is less sensitive. It is positive in 20 to 50 percent of cases, being much more likely to occur in patients with parenchymal disease.

On histological examination, the presence of pleural granulomas is virtually diagnostic of tuberculous pleuritis. Caseation and demonstration of acid-fast bacilli are not required, although noncaseating pleural granulomas can occasionally be seen in other disorders such as, fungal disease, tularemia, sarcoidosis and rheumatoid lung disease. The initial pleural biopsy in tuberculous pleuritis is positive in approximately 70 percent of cases. A greater number of biopsies taken at a single session (6 or more), or multiple, separate biopsy procedures can increase the sensitivity to 80 percent. However, multiple biopsy sessions are usually not necessary because the combination of histological examination and culture of the initial pleural biopsy is over 90 percent sensitive. This combination is regarded as the most sensitive diagnostic test for pleural tuberculosis.

Pleural fluid analysis:

Characteristics of the pleural fluid – The effusion in tuberculous pleuritis is straw-colored in more than 80 percent of cases. It has the following characteristics:

- The fluid is invariably an exudate. The protein concentration is usually above 3.0 g/dL, and is greater than 5.0 g/dL in 50 to 77 percent of cases.
- The pleural fluid LDH level is usually elevated
- A low pH and glucose concentration can occur. The pleural fluid glucose concentration in tuberculous pleurisy is usually between 60 and 100 mg/dL, with levels below 50 mg/dL being found in only seven to twenty percent of effusions.

Extremely low levels can occur (<30 mg/dL), but are rare and usually associated with tuberculous empyema. The pleural fluid pH is virtually always less than 7.40, with 20 percent of patients having a pH below 7.30.

- The nucleated cell count in the effusion is usually between 1000 and 6000/mm3. It is lymphocyte predominant in 60 to 90 percent of cases; the remaining patients have neutrophil predominance, in which the neutrophils occasionally account for more than 90 percent of the cells. Lymphocytes predominate in subacute and chronic tuberculous effusions. In patients with symptoms of less than two weeks duration, neutrophils predominate, an observation which is in accord with the findings in experimental pleurisy. The time course for the transition from neutrophils to lymphocytes in humans is unknown, if serial thoracenteses are performed, the differential count reveals a change to predominantly small lymphocytes.

The pleural fluid in TB pleuritis rarely contains more than five percent mesothelial cells. Lack of mesothelial cells is also not diagnostic for TB as any condition in which the pleural surface is extensively involved will lead to absence of mesothelial cell. Prominent eosinophil infiltration is also uncommon. The presence of more than 10 percent eosinophils usually excludes the diagnosis of tuberculous pleuritis unless the patient has had a previous pneumothorax or thoracentesis. (Previous thoracentesis and or pneumothorax can introduce air and or blood which leads to the pleural fluid eosinophilia).

Tuberculin skin testing – A negative skin test does not rule out the diagnosis of tuberculous pleuritis as in about 30% of patient tuberculin skin testing will be negative. If the patient is retested in about 2 months after the onset of symptoms, the skin test is invariably positive.
One possible explanation for the initial negative skin test is the suppression of sensitized T-cells in the peripheral circulation and skin by circulating adherent mononuclear cells (chiefly monocytes, not classic CD8 suppressor cells). These monocytes are known to suppress antigen-induced lymphocyte blastogenesis and the production of interleukin-2. Second, there may be sequestration of reactive T lymphocytes in the pleural space.11,12

Although in countries where tuberculous disease is uncommon, the positive tuberculin skin test will be a valuable information in narrowing down the differential diagnosis. In countries like Pakistan where mycobacterial disease is endemic, the tuberculin skin testing should not be used as a diagnostic tool for tuberculosis.

Special tests – Several special tests, such as pleural fluid adenosine deaminase and lysozyme concentrations, have been investigated for use in diagnosing tuberculous pleural effusions. None are routinely used at present.

Adenosine deaminase – Pleural fluid adenosine deaminase (ADA) concentrations are elevated in tuberculous pleural effusions. Some large series suggest that ADA is 100 percent sensitive and 95 to 97 percent specific when a value above 45 to 60 U/L is found.13 In a 1999 analysis of 216 patients with pleural effusion, a receiver operating characteristic curve identified the best cutoff at 60 U/L, yielding an excellent sensitivity (0.95), specificity (0.96), positive predictive value (0.96), and negative predictive value (0.95). Specificity is decreased by high ADA levels that occasionally occur in other conditions such as rheumatoid effusion, empyema, mesothelioma, lung cancer, parapneumonic effusion, and hematologic malignancies.14 Choosing a lower ADA cutoff value will increase sensitivity at the expense of specificity.14,16

These variable findings may reflect in part failure to distinguish between the two principal isoenzymes, ADA-1 and ADA-2. ADA-2 is increased in tuberculous effusions, while ADA-1 rises in empyemas.17 Most studies have reported only the total ADA level.13,16,17

At present, pleural fluid ADA remains "an aid to differential diagnosis," as it was originally described in 1978.15 It is most useful in the 10 percent of patients with tuberculous pleurisy who have negative standard diagnostic studies, i.e., negative pleural histology and culture.16,19

Lysozyme – Pleural fluid lysozyme concentrations are greater than 15 mg/dL in over 80 percent of tuberculous pleural effusions.20 However, the highest concentrations are found in empyemas. Another limitation to this test is the overlap between tuberculous and malignant effusions.

The pleural fluid-to-serum lysozyme ratio may be more useful than the absolute value. If empyemas are excluded, a ratio above 1.2 has been reported to have 100 percent sensitivity for tuberculous effusions and 95 percent specificity.20

Gamma interferon – Measurement of pleural fluid gamma interferon also may be useful. A gamma interferon concentration above 140 pg/mL had a sensitivity of 94 percent and a specificity of 92 percent for detecting tuberculous effusions when tested in 145 patients.21 A second study in 66 patients with exudative, lymphocytic pleural effusions found a sensitivity of 95 percent and a specificity of 96 percent for the test when a cut-off value of 240 pg/mL was employed.22,23

Polymerase chain reaction – Polymerase chain reaction has a sensitivity of only 42 to 81 percent and is expensive. Its use in this setting is not currently recommended. In establishing the diagnosis of TB-pleuritis, it was not found superior either to pleural fluid ADA or interferon gamma levels.24

Natural history:

In most patients the pleural effusion will subside without treatment within 2-4 months; only to return as active tuberculosis at a later date in about 43-65%. There are no predicting features including the size of the initial effusion or the presence or absence of parenchymal disease on a CXR.

Recommendation:

Tuberculous pleural effusion is third most common presentation of tuberculous disease after pulmonary and lymph node involvement. Pakistan ranked 8th among countries with the highest disease burden. Any exudate pleural effusion either acute or chronic especially with lymphocytosis (neutrophil: lymphocyte > 0.75) should be treated as tuberculosis until proven otherwise. At present special tests for the diagnosis of tuberculous pleuritis are not available in Pakistan. Pleural biopsy should be performed and only if either AFB smear or the culture is positive or the biopsy demonstrates granulomas the treatment of tuberculosis should be started.

Pearls:

- Extra-abdominal causes can lead to significant abdominal pain.
- All acute exudate effusion are not parapneumonic
- Pleural fluid neutrophilia does not rule out tuberculous pleuritis
- Pleural fluid lymphocytosis is not pathognomonic for tuberculous pleuritis
- Pleural biopsy is diagnostic in acute tuberculous effusion
References

Bacteremia Associated with Central Line Infection by Chryseomonas Luteola in a Case of Recurrent Meningiomas.

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Case Summary

A 52 years old diabetic and asthmatic lady was admitted in the Neurosurgery service with a post-operative wound infection 10 days following removal of meningioma. The patient had a history of recurrent meningiomas for which she had undergone multiple surgeries during the past ten years.

On admission, the patient was febrile and drowsy. There surgical wound site over the scalp was swollen, exuding a purulent discharge. Subsequently, a lumbar drain was inserted for CSF drainage, the yellowish discharge from the wound was sent for culture, which grew Streptococcus pyogenes for which I/V Ceftriaxone was started. The patient improved and remained stable till about the 25th day of hospital stay when she developed fever, chest infiltrates as well as copious purulent discharge from the wound.

Due to rapid deterioration in patient’s condition she was shifted to ICU. Piperacillin tazobactam was started and lumbar drain was removed. The scalp wound was re-explored and a flap closure was done; an epidural drain was inserted for CSF drainage. As the patient did not improve clinically, all antibiotics were stopped and patient was rescreened for infection. One set of blood culture drown from a peripheral vein and the tip of pulmonary artery catheter grew Chryseomonas luteola. This organism was sensitive only to Ofloxacin and the patient’s antibiotic regimen was changed to Ofloxacin along with Aztreonam and Amikacin. The patient gradually improved on this regimen, was moved out of the ICU and subsequently managed in the ward.

Discussion

Chryseomonas (CD4 group Ve-1) are normal inhabitant of soil and environment usually regarded as a saprophyte or commensal rarely recorded as pathogenic to humans. Previously they were named as Pseudomonas luteola due to resemblance with Pseudomonas. Most victims are immunocompromised or immunocompetent patients with a foreign body inserted.

Chryseomonas luteola is a non-sporing non-motile gram negative rod with a distinct yellow orange pigment. Growth on MacConkey’s agar shows rough or wrinkled colonies, biochemically they are non lactose fermenters, oxidase negative and catalase positive. Chryseomonas luteola has been reported to cause septicemia, bacteremia in cases of granulomatous hepatitis, prosthetic valve endocarditis, meningitis associated with intracranial prosthesis and in patients with indwelling intra-vascular catheters. Bacteremia with Chryseomonas luteola has been noted in immunocompromised patients, especially those with an indwelling catheters.

Few clinical case reports have been published regarding isolation of Chryseomonas luteola. In one such published report by Ghosh this organism was isolated from a superficial cutaneous infection on face in an AIDS patient. Another report of Chryseomonas related facial cellulites was reported by Rastogi et al in a homosexual HIV-negative male.

Rahav et al. in his case series reported four cases of Chryseomonas luteola, in which two of the cases were associated with the presence of a central line; one strain was isolated from an infected hip joint and another one from ascitic fluid of a patient with colonic carcinoma.

Most clinical isolates of Chryseomonas luteola reported so far have been resistant to ampicillin, tetracyclines, trimethoprim-sulfamethoxazole and first and second generation cephalosporins, but susceptible to third generation cephalosporins, mezlocillin, imipenam, aminoglycosides and quinolones.

In the present case, though the patient was not labeled as immunocompromised but history of steroid therapy in past multiple surgeries for recurrent meningiomas, with prolonged hospital stay make her immune status compromised.

In the present case, the patient was not a labeled as immunocompromised and was not on any regular immunosuppressive therapy when she developed this infection.

Chryseomonas luteola was isolated both from the pulmonary catheter tip and blood culture, suggesting bacteremia secondary to line colonization. Like all previously reported Chryseomonas luteola, our isolate was sensitive to fluoroquinolones and patient was treated with Ciprofloxacin and recovered from the infection.

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Isolation of a rare organism like *Chryseomonas luteola* underscores a need for clinicians as well as laboratories to be aware of the importance of such organisms as pathogens, particularly in critically ill or immunocompromised patients. With increasing numbers of patients with immunodeficiencies with long term indwelling catheters and prostheses, and increasing use of immunosuppressive therapy for various conditions, isolation of such organisms in clinical samples should be evaluated critically and special care must be taken before disregarding them as contaminants.

References

A 30 Year Old Asian Male with Right Sided Lower Abdominal Pain and Fever

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A 30-year-old Asian male presented with severe right-sided lower abdominal pain, fever, nausea and vomiting for the last 2 days. He had no significant prior medical history. On physical examination, he had a temperature of 39°C. The abdomen was soft with normal bowel sounds; however, right iliac fossa was tender. The liver span was 15 cm at the right mid-clavicular line. The rest of the findings from the physical examination were normal. Stool tested trace positive for occult heme. Levels of routine serum electrolytes and of routine blood tests of liver function were within normal limits. The hemoglobin was 12.6 gm/mL and the leukocyte count was 19,600/ml with 57% neutrophils, 28% band forms and 4% eosinophils. Abdominal roentgenogram was within normal limits. No appendicolith was present. A diagnosis of acute appendicitis was made. He underwent appendicectomy and specimen was sent for histopathology. On gross inspection appendix appeared dilated and measured 5x1.5 cms. On sectioning lumen was filled with necrotic material and mucosa was sloughed. Sections from the resection margin, middle part and base of appendix were submitted. Microscopic examination revealed extensive surface ulceration with transmural severe acute and chronic non-specific inflammation. A profound flask-shaped ulcer containing exudative necrotic material with fibrin was seen in which numerous large, round to oval organisms were identified containing intracytoplasmic erythrocytes. Invasion of venules and lymphatics by these organisms was also appreciated.

Legends

1. H&E Stain X 40. Showing intravascular rounded organisms along with luminal necrosis.
2. Periodic acid-Schiff stain X 40 outlines the organisms.

What is your diagnosis?
IDSP Activities - September to December 2004

- **September 25.** A “Walk for Rabies awareness” was organized by the IDSP, PMA, CDGK and Helpline Forum. This walk was led by Mr. Niamatullah Khan, City Nazim, Karachi. It was important in highlighting the problems associated with stray dogs and dog bites – prevention and control in Karachi.

- **November 20, 2004.** HIV –AIDS Conference. National AIDS Control Programme (NACP) and Infectious Diseases Society of Pakistan (IDSP) organized a conference at Pearl-Continental Hotel, Lahore. The Program summary and speaker was as listed:

  - Welcome Note: Asma Bokhari, Chairperson NACP
  - Epidemiology of HIV in Pakistan: Sharaf Ali Shah
  - A case series of over 100 patients: Naseem Salahuddin
  - Diagnostic aspects: Mteen Izhar
  - Introduction to anti-retroviral drugs: Ferheen Ali
  - Adverse effects and interactions of ARV: Yasser Hussain
  - When to start therapy and how?: Aslam Khan
  - When to change therapy?: Mahmud Javid
  - Special issues in children: Anita Zaidi
  - Opportunistic infections - prevention and Rx: Shaukat Bangash
  - Post-exposure prophylaxis: Sobia Qazi
  - Tuberculosis and HIV: Mansur Javaid
  - Counting Number of Dogs and Dog Bites: Dr. Aamir Khan, Assistant & Director R&D, Johns Hopkins University, USA
  - Closing Address: Faisal Sultan

- **December 21, 2004.** Seminar on “Dog bite and Rabies in Karachi: how should we solve the problem?” **Organized by IDSP and City District Government Karachi (CDGK)** Auditorium, Civic Center, Karachi. The program was as listed below. A short video film on Rabies was also shown

  - Moderator: Dr. Nayyer ul Islam, Asst. Prof. of Medicine, Abbasi Shaheed Hospital
  - Stating the Problem of Rabies in Karachi: Dr. Naseem Salahuddin, Member, WHO Expert Panel Committee
  - Seeking Solutions
    - Thailand’s success story: what can we learn?: Dr. Altaf Ahmed, Consultant Clinical Microbiologist, Liaquat National Hospital
    - Providing Optimum Care at Low Cost: Dr. Syed Ali Sardar, Clinical Fellow A & E, Liaquat National Hospital
    - Counting Number of Dogs and Dog Bites: Dr. Aamir Khan, Assistant & Director R&D, Johns Hopkins University, USA
    - Dog Population Control
      - How we can all work together?: Dr. Naseem Salahuddin
      - Suggestions invited
  - Concluding Remarks, Niamatullah Khan, City Nazim, Karachi.
PHOTO QUIZ

Answer to Photo quiz

Amoebic Appendicitis

Discussion

Entameba histolytica is an enteric protozoan that infects 10% of the world’s population resulting in 100,000 deaths per year. Although its prevalence is highest in poor developing countries having the lowest level of sanitation, the convenience of modern travel, high rates of emigration, and existence of high-risk groups in developing countries require physicians throughout the world be familiar with the diverse clinical syndromes resulting from Entameba histolytica infection. Entameba histolytica infection presents mainly in 2 clinical forms as intestinal and extraintestinal disease. Intestinal disease occurs in 4 major types including asymptomatic colonization (cyst passage), acute amoebic colitis, fulminant colitis, and ameboma. Stricture formation, ulcerative post dysenteric colitis, intussusception, extra intestinal dissemination, massive hemorrhage and intestinal perforation are the main complications of intestinal amebiasis. E.histolytica cysts, which have a chitin wall and four nuclei, are the infectious form because they are resistant to gastric acid. Amebiasis begins as a primary infection of the colon by ingestion of the encysted protozoan E.histolytica in contaminated food or water. Excystation occurs in small bowel and the resultant trophozoites are carried down the small intestine to settle in the most static areas, typically the cecum and appendix. When E.histolytica attach to the colonic epithelium, lyses colonic epithelial cells, and invade the bowel wall.

The infection is asymptomatic until the invasion occurs. Amebiasis most frequently involves the cecum and ascending colon, followed in order by the sigmoid, rectum, and appendix. In severe full-blown cases, however, the entire colon is involved. Ameobae can mimic the appearance of macrophages because of their comparable size and large number of vacuoles; the parasites, however, have a smaller nucleus, which contains a large karyosome. Ameobae invade the crypts of the colonic glands, burrow through the tunica propria, and are halted by the muscularis mucosae. There the amoebae fan out laterally to create a flask-shaped ulcer with a narrow neck and broad base. As the lesion progresses, the overlying surface mucosa is deprived of its blood supply and sloughs. The earliest amebic lesions show neutrophilic infiltrates in the mucosa, which later develop into ulcers that contain few host inflammatory cells and areas of extensive liquefactive necrosis. The mucosa between ulcers is often normal or mildly inflamed. Amebiasis spreads to other areas of body such as to liver, lungs and brain through amebic invasion of venules or lymphatics.

Intestinal invasion typically produces acute attacks of diarrhoea with loose, mucoid, bloodstained stools (amebic dysentery), fever, headache and nausea. Abdominal discomfort can range from mild discomfort to the more common gripping pain.

The association of appendicitis and amebiasis is an exceptionally rare occurrence with a few case reports series in the literature. Luminal obstruction is accepted universally as the prime cause of appendicitis, and the association of appendicitis and parasites raises the possibility of a causative relationship between E.histolytica and appendicitis. This pathogenic process can affect the appendix both primarily and secondarily. Widespread caecal disease can lead to primary appendicidal involvement or generalized bowel congestion can contribute to secondary appendiceal swelling. Patients who present with symptoms and signs localized to the right lower quadrant, particularly those with recent travel to endemic areas, should have clinical tests for amebiasis, including a serologic test for ameba and examination of specimens from stool or from endoscopic biopsies. Timely appropriate therapy before the development of significant abdominal findings is typically curative.

References


Infectious Diseases Journal of Pakistan
INSTRUCTIONS FOR AUTHORS

Instructions for Authors

Scope
The Infectious Diseases Society of Pakistan sponsors the Infectious Disease Journal of Pakistan (IDJP). The Journal accepts Original Articles, Review Articles, Brief Reports, Case Reports, Short Communications, Letter to the Editor and Notes and News in the fields of Microbiology, Infectious Diseases; with laboratory, clinical, or epidemiological aspects.

Criteria for publication
All articles are peer reviewed by the IDSP panel of reviewers. The Editors review Correspondence. Authors may also submit the names and contact informations of 2 persons who potentially could serve as unbiased and expert reviewers for their manuscript, but IDSP reserves the right of final selection.

Submission of the Manuscript
Manuscripts must be formatted according to submission guidelines given below, which are in accordance with the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (originally published in N Engl J Med 1997;336:309-15). The complete document appears at www.icmje.org.

Please submit one complete copy of the manuscript and all enclosures to The Editor, Infectious Diseases Journal of Pakistan, Department of Pathology and Microbiology, The Aga Khan University, Stadium Road, P.O. Box 3500, Karachi 74800, Pakistan. An electronic copy of the manuscript must also be sent to masim.beg@aku.edu. All manuscripts submitted to IDJP must be accompanied by an Authorship Declaration stating that ‘The authors confirm that the manuscript, the title of which is given, is original and has not been submitted elsewhere. Each author acknowledges that he/she has contributed in a substantial way to the work described in the manuscript and its preparation’.

Manuscript Categories

I. Original Articles

Articles should report original work in the fields of microbiology and infection.

Title page
This should list the (i) title of the article, (ii) the full names of each author with highest academic degree(s), institutional addresses and email addresses of all authors. (iii) The corresponding author should also be indicated with his/her name, address, telephone, fax number and e-mail address. (iv) A short running title of not more than 40 characters (count letters and spaces) placed at the foot end of the title page.

Abstract
Abstract should not exceed 200 words and must be structured in to separate sections headed Background, Results and Conclusions. Please do not use abbreviations or cite references in the abstract. A short list of four to five key words should be provided to facilitate.

Background
The section must clearly state the background to the research and its aims. The section should end with a very brief statement of what is being reported in the article.

Materials and Methods

Please provide details of subject selection (patients or experimental animals). Details must be sufficient to allow other workers to reproduce the results. The design of study and details of interventions used must be clearly described. Identify precisely all drugs and chemicals used, including generic name(s) and route(s) of administration.

Results

Present results in logical sequences in the text, tables and illustrations. Articles can have a maximum of 5 illustrations (in a combination of figures and tables) per article.

Discussion

Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat the details from the Results section. Discuss the implications of the findings and their limitations. Link the conclusions with the goals of the study but avoid unqualified statements and conclusion not completely supported by your data.

Acknowledgments

Acknowledge any sources of support, in the form of grants, equipment or technical assistance.

Please see below for format of References, Figures and Tables.
II. Review Articles

Authoritative and state of the art review articles on topical issues are also published, with a word limit of 2000. These should be comprehensive and fully referenced. Articles should contain an Abstract; Main Text divided into sections, Conclusions and References.

III. Brief Reports

Short clinical and laboratory observations are included as Brief Reports. The text should contain no more than 1000 words, two illustrations or tables and up to 10 references.

IV. Case Reports

Instructive cases with a message are published as case reports. Routine syndromes or rare entities without unusual or new features are invariably rejected. The text should contain no more than 1000 words, two illustrations or tables and up to 10 references. The authorship should not exceed 3-4 persons.

V. Letter to the Editor

These may relate to material published in the IDJP, topic of interest pertaining to infectious diseases, and/or unusual clinical observations. A letter should not be more than 300 words, one figure and 3-5 references.

VI. News and Views

Informative, breaking news updates in infectious diseases from around the world (approx. 200 words).

VII. Notices

Announcements of conferences, symposia or meetings may be sent for publication at least 12 weeks in advance of the meeting date. Details of programs should not be included.

References

Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals (in superscript). References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification of the particular table or illustration. Bibliography should be given in order.


Tables and Figures

Data reported either in a table or in a figure should be illustrative of information reported in the text, but should not be redundant with the text. Each table must be presented on a separate sheet of paper and numbered in order of appearance in the text. Table should be numbered consecutively in Arabic numerals. Tables and Figures legends should be self explanatory with adequate headings and footnotes.

Illustrations

Illustrations should be numbered, given suitable legends and marked lightly on the back with the author’s name and the top edge indicated. Original drawings may be submitted although high quality glossy photographs are preferable. They should be kept separate from the text. If possible, figures should be submitted in electronic format as either a TIFF (tagged image file format) or JPEG format.

Minimum resolution for scanned artwork is:

* Black & white line illustration (eg graphs): 600 dpi
* Black & white halftone illustrations (eg photographs): 300 dpi
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