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ARTICLE

Childhood tuberculosis in the Western world

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Childhood tuberculosis in the Western world

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AUTHORS' SUMMARY

Tuberculosis (TB) is a major problem worldwide and may be the most common infectious disease. It has been calculated that there are 1.3 million new cases annually and 460,000 deaths in children alone (12). The overwhelming burden of TB is in the developing world. However, it is still a problem in the Western countries, and has generated a number of recent reports from different centers (1,2,4). These reports show that TB in children in the West comes with certain risk factors that differ, to some extent, from those in developing countries. This review article concentrates on childhood TB in the Western world, its occurrence, risk factors, management and preventive measures (8,9,10).

The timetable of tuberculosis

The natural history of childhood tuberculosis was well described by pediatricians early in the 20th century, such as Dorothy Price in Ireland and Arvid Wallgren in Sweden (3,19). Today, primary TB is found at all ages, and, second to infants, young adults may be the most severely affected, as described in a report from the Faeroes in the 1930s (20).

Following exposure, the incubation period is usually 5 to 6 weeks, but could be as short as 3 weeks or as long as 3 months. In the majority of cases, there is then an immunological reaction and an unnoticeable primary infection that converts into latent tuberculosis (LTB, see below). LTB can later reactivate to disease. In 5 to 10% of individuals, probably exposed to a high infectious dose, especially virulent bacterial strains, or

genetically predisposed, disease develops. The manifestation of the disease depends on the age of the patients and the stage of infection. From the primary complex in the lung, lymphohematogenous spread leads to dissemination. In most cases, spread is initially to other parts of the lungs, especially apically, where growth conditions are favourable. In a minority of cases, other organs are involved. Bronchogenic spread, often with catastrophic consequences if untreated, occurs when a bronchial wall is eroded by a caseous nodule and necrotic material discharged into the lumen.

It is important to realize that the risk of acquiring infection is not the same as the risk of developing disease. The risk of acquiring infection is related to the situation of exposure to these individuals (either at home or visiting their parents'

country of origin). The risk of developing disease is related to certain risk factors, such as young age and immunosuppression including HIV infection (Table 1). In the Western world today, both disease and infection are mostly seen in immigrants from high-prevalence countries. The increased risk is then due to active disease on arrival, reactivation of latent infection, and – for both previously uninfected adults and children born in the new countries – exposure to these individuals. Overcrowding and poverty have not been as important as in the developing world.

Symptoms

Tuberculosis has been considered capable of mimicking many diseases and can manifest itself in practically any location. In reality, a few common presentations dominate, especially in children. The most common symptoms are fever, abdominal pain, anorexia and weight loss. These symptoms are unspecific in children with various pathogens as possible etiology (3). In Ireland in the 1930s, influenza and typhoid fever were considered the most important differential diagnoses (19). Clinical symptoms are more often seen in younger than in older children.

It is important to note that early in the course, even though there is a primary focus in the lung, cough is not a prominent symptom. Respiratory symptoms will occur if a primary infection in the lung persists (11). Except for infiltrates, the most typical radiological findings are then enlargement of mediastinal lymph glands. The primary (Ghon) complex consists of the primary focus in the lung parenchyma together with the enlarged regional lymph glands in the lung hilus. The enlarged lymph nodes can compress the airways and cause wheezing, which may be the main presenting symptom. In adolescents, reactivation can occur. The symptoms are then more like those of adults, i.e., cough, fever and chest pain. Pleurisy,

Table 1. Risk factors for tuberculosis in children living in the Western world

Risk of acquiring infection

Close and long contact with a contagious adult person

Risk environment for exposure

Foreign-born in a high incidence country

Living in an environment with many foreign-born adults

Prolonged visit (> 1 year) to home country

Living in high risk groups, such as with drug addicts or prisoners if incidence is high in these groups

Risk of developing disease if infected

Young age (< 5 years)

Young adulthood?

Immunosuppression from disease and/or treatment

HIV

Previous inadequate treatment

be a common, sometimes self-limiting, symptom in adolescents. It was often seen 3 to 6 months following exposure, and was considered more of a hypersensitivity reaction comparable to erythema nodosum (3).

Disseminated tuberculosis in young infants can occur as early as three weeks following exposure, even before the tuberculin skin test (TST) becomes positive. There is then a general dissemination with a miliary spread in the lungs, liver and spleen, leading to hepatosplenomegaly. General symptoms and respiratory distress are then present even if there is often a discrepancy between clinical findings and the extensive x-ray changes. Tuberculosis meningitis is a dreaded result of hematogenous spread. Hematogenous spread to the skeleton is also often a relatively early (6 to 9 months after infection) manifestation.

Enlargement of lymph nodes, most often in the cervical region, occurs as lymphogenic spread takes place. Besides enlarged lymph nodes that can rupture and cause draining fistula, there are few other symptoms, even though following the initiation of therapy there may be improvement of previously unrecognized, diffuse symptoms such as weight loss and **fatigue**.

tuberculosis in almost any organ that can sometimes manifest itself much later, often in adulthood. The primary complex in the lung may then no longer be visible radiologically.

Diagnosis

For nearly 100 years, the diagnosis of tuberculosis has relied, and still relies today, on the fulfillment of at least three of the following four criteria: 1) compatible symptoms; 2) close exposure to a contagious case of tuberculosis (usually an adult with pulmonary reactivation living in the same household); 3) compatible pulmonary x-ray findings; and 4) a positive TST. Ideally, the diagnosis is confirmed by a positive culture of either *Mycobacterium tuberculosis* or, rarely, *M.bovis*.

Additional investigations

As for many other diseases, history and physical examination are often supplemented by laboratory tests and radiology. In a child with clinical TB, laboratory tests may demonstrate a slight anemia, a raised ESR, and moderately elevated CRP. However, the changes in blood chemistry are extremely variable and may be misleadingly mild or completely absent in the face of extensive disease.

Typical radiological findings have been described for many organs, such as brain tuberculoma or skeletal changes. In the lung, hilar enlargement and atelectasis in combination with segmental hyperinflation or collapse (“the collapse-consolidation lesion”) are characteristic. They are caused by a combination of lung disease and mechanical changes due to airway obstruction by the lymph nodes. Cavitations may be found at reactivation of LTB or develop directly following primary infection.

In many instances, the right diagnosis can be suggested by microscopic investigation of biopsies, especially of lymph nodes, showing typical granulomas and the presence of acid-fast bacilli. Ideally, these biopsies should also be submitted for culture and, if available, PCR. Also, cytologic examination frequently reveals diagnostic changes. A warning finger has sometimes been raised against the cytologic puncture of suspected TB glands, but in our experience such fear is unwarranted. On the contrary, even clinically innocuous nodes can be punctured for cytologic examination in patients with epidemiological and clinical findings indicative of TB. Should TB be present, eventual puncture channel infection will rapidly heal during medical treatment.

In the diagnosis of pulmonary TB, bacteriological confirmation by sputum culture is the gold standard. Due to the low bacterial load in primary infection and the difficulties experienced by small children in producing sputum, culture has been difficult in children. Early morning gastric aspirates have been considered necessary, but, even so, the yield is usually only around 50% (8,9,10). Fortunately, in the youngest children the yield is often better than in somewhat older individuals. To get a better picture of TB involvement, bronchoscopy has been considered useful. However, the culture yield from bronchoalveolar lavage is usually inferior to that of gastric lavage, at least in prepubertal children, and a confirmation

has been achieved in only 10 to 20% (5). At present, early morning gastric lavage is considered impractical, and recent studies have shown that outpatient gastric lavage is a reasonable alternative (6). In our practice, experienced pediatric nurses and physiotherapists have been able to obtain diagnostic sputum samples from children of around 6 to 7 years of age, thereby avoiding gastric lavage.

Culture is still a time-consuming process but is necessary to find drug resistance. In this situation, PCR is quick and reliable while awaiting confirmation by culture (7). Culture, however, remains the gold standard, and those specimens from the respiratory tract that eventually give positive cultures are positive by direct microscopy and PCR in about 50% and 90% of cases, respectively.

Skin test

In the work-up of a child with suspected tuberculosis, a TST is usually performed. TST can be performed in many ways, but nowadays the method of Mantoux is almost exclusively used. Two TU (in the US, 5 TU) of purified protein derivative of tuberculin (PPD) are applied intradermally in the dorsum of the left arm. The size of the induration (not erythema) is read after 48–72 hours. There are both false positive and false negative reactions. Most children are negative a few years after BCG vaccination, and those that are positive rarely have an induration of more than 10 mm. An induration of more than 10 mm in vaccinated children is indicative of exposure to mycobacteria, preferentially *M. tuberculosis*. In unvaccinated people, a reaction of more than 5 mm is positive. If the child is tested during the incubation period, the initial skin test may be negative and convert to positive within 2 to 3 months. Such conversion may be impossible to distinguish from the “booster phenomenon”, where a second TST in a vaccinated individual may give a significantly larger reaction (21).

According to the literature, false negative reactions are seen in 10 to 20% of patients (in HIV positive patients, up to 80%) with tuberculosis. In our experience, false negative reactions are rare, possibly because patients get medical attention at an early stage of disease. It is important to realize that the TST should not be used as a marker of protective immunity against tuberculosis.

Reactions measuring 6 to 10 mm are sometimes seen in patients sensitized to non-tuberculous mycobacteria other than BCG. Such reactions are especially important in countries with a low prevalence of tuberculosis, and in Sweden such sensitization undoubtedly accounts for almost all reactions of this size in the native, unvaccinated population. In one study, 2 to 3% of all children in western Sweden were sensitized to non-tuberculous mycobacteria, with TSTs more than 6 mm (18).

Repeated testing in non-sensitized children will give persistently negative results. In people immunized with BCG several times, a practice seen in the former Soviet Union among other countries, reactions up to 15 mm can be seen (22).

Latent tuberculosis

Latent tuberculosis (LTB) was previously called “TB infection” in contrast to “TB disease”. The condition is defined by the following criteria: 1) previous exposure to *M. tuberculosis*; 2) positive TST; 3) normal chest x-ray, or “old” changes compatible with healed primary infection; and 4) no clinical evidence of disease. The distinction between LTB and early or mild primary disease can sometimes be difficult to make. It is generally taught that during the first two years after exposure approximately 5% of cases develop clinical disease, followed by another 5% in subsequent years. In many countries, most adult cases of TB consist of such reactivation. The risk of reactivation to active disease is strongly influenced by risk factors and may in HIV-infected individuals approach 10 to 20% per year. Treatment of

LTB is comparatively easy since the number of bacteria is low and single drug therapy often acceptable. With treatment, the risk of reactivation is reduced to nearly zero.

Even with a relatively high specificity of the TST, the number of false positive reactions will be unacceptably high if a population with a low prevalence of TB infection is screened. Therefore only targeted testing should take place in Western countries, including diagnostic testing, environmental control, and screening of immigrants from high prevalence countries. Such screening is done in Stockholm by the child health centers and in the schools. If a test is positive (>6 mm), the child is referred to a pediatric center with experience of tuberculosis. Following a careful history, including possibility of exposure and physical examination (including examining for lymphadenitis) and chest x-ray, either a presumptive diagnosis of LTB is made or the reaction is considered due to exposure to non-tuberculous mycobacteria, including BCG. It is extremely important to remember that BCG vaccination offers only limited protection, that 70 to 80% of BCG-vaccinated individuals have a negative TST, and that a TST reading of >10 mm should not be ascribed to previous BCG vaccination.

Treatment

Treatment is mandatory for cure of clinical TB. Treatment is offered for latent TB, especially if found in the environmental control around a contagious (smear-positive) index case.

Treatment of clinical disease is usually started with a combination of isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) when the susceptibility pattern of the strain of the adult index case is known. If the susceptibility of the index case is unknown or the clinical course is complicated, a combination of four drugs is recommended usually with ethambutol (EMB) as the fourth drug (Table 2). PZA is given during the first two months, after which little added ther-

Table 2. TB therapy in children

Drug	Dose	Max	Side effects	Remark
INH (Tibinide)	5–15 mg/kg	300	Rarely* hepatotoxicity, peripheral neuropathy	Pyridoxin supplement to: Breastfed infants Adolescents Malnourished
Rifampicin (Rimactan, Rifadin)	10–20 mg/kg	600	Rarely* hepatotoxicity	Red/orange discoloration of urine
Pyrazinamide (Zinamide, PZA CIBA)	15–30 mg/kg	2 g	Rarely* hepatotoxicity	Usually only the first two months of treatment
Ethambutol (Myambutol)	15–25 mg/kg		Rarely vision disturbance	

* risk of hepatotoxicity increases when combinations are used

The formulations and tablet strengths are mainly suitable for adults, and medication of young children is difficult. Recently, through the help of Orphan Drugs, soluble formulations have been made available. Rimactazid Paed 60/60 Intermittent® contains a fixed combination of INH (60 mg) + RIF (60 mg), and Rimcure Paed 3-FDC® contains INH (30 mg) + RIF (60 mg) + PZA (120 mg).

Compliance is essential for the outcome, and regular follow-up and contact with the patient and his carer is important. Despite this, if compliance is questionable, directly observed therapy has to be considered. In directly observed therapy, treatment is given three times a week.

Side effects are uncommon in children compared to adults and seldom lead to the discontinuation of therapy. Transient elevation of liver enzymes can be seen, especially at the beginning of therapy when INH, RIF and PZA are used in combination. In a review of patients seen by us over 20 years, 5% had some kind of side effects including dermatitis and renal impairment (2).

The duration of treatment is six months. Improvement of general condition and well-being is seen after 1 to 3

fever, radiologic changes or the size of lymphadenitis takes much longer to resolve. If the chest x-ray is clear after a few weeks or the lymphadenitis has disappeared, the most likely diagnosis is an ordinary bacterial or viral infection and not TB.

As mentioned previously, LTB has a much lower burden of bacteria and can usually be managed effectively by one drug, usually INH. The duration of treatment is 9 months. Drug combinations have been tried in order to achieve a shorter treatment duration. One such treatment comes from studies in adult HIV-positive patients where RIF and PZA given daily for 2 months were as effective as 12 months of INH. Another alternative, used in the UK, is RIF and INH for 3 months (13). Combination therapy is more expensive than INH for 9 months.

Exposure to a contagious case, usually a family member, is enough to prompt treatment of certain groups of young children. It is often recommended that exposed children under 5 years, after obtaining chest x-ray, are treated for LTB until the incubation period has expired. If the TST is negative and there is no further exposure, therapy can be

discontinued. New-born infants exposed to an adult with TB need special consideration. It is only contagious (smear or culture positive) disease that can be a threat. If the infant has been exposed, INH prophylaxis (or other drug treatment if there is resistance) is recommended until the baby can be tested at the end of the incubation period *and* has attained an age of more than 6 months (false negative reactions are common before that age). It is important not to vaccinate during the incubation period since such vaccination makes it impossible to determine if the baby has been infected or not. A mother with localized extra-pulmonary or latent tuberculosis cannot transmit disease. In the rare event that the mother has disseminated disease, such as miliary TB or TB meningitis during pregnancy, there is a risk of congenital TB, and the infant and placenta should be observed and examined for evidence of disease (16).

Prevention

It is important to direct educational effort towards health care personnel so that new cases of active tuberculosis are suspected and diagnosed as soon as possible, and an environmental control placed around the index case. In certain situations, it can be appropriate to use targeted screening of high-risk populations, such as newly arrived refugees from countries with a high prevalence of tuberculosis. Finally, BCG immunization is a way of preventing severe complications of primary tuberculosis, especially among infants and young children.

TB in young children should be rare if enough attention is paid to the adult patient. In our experience, the most common presentation has been fever without localizing signs, with very little if any respiratory symptoms initially. In adolescents, the situation is somewhat different since the disease can be reactivated from an earlier exposure causing significant respiratory symptoms. Such reactivation can be prevented by targeted screening and treatment of LTB in refugees.

Today, environmental control is concentrated in special units with experience of childhood tuberculosis. All children, especially infants, should be examined as soon as possible if the index case is contagious. As mentioned above, many children can be relatively asymptomatic in spite of extensive changes, and the disease can be missed when questions such as “is your child well?” are asked. All children exposed to an adult with tuberculosis are now examined even if the index case is not contagious. In this situation, the purpose of investigation is to ascertain that both mother and child have not been exposed to the same source.

In the Stockholm area today, targeted screening is done for all children from a country with high prevalence of TB, and is performed by the child and school health centers. If the TST is positive, the children are referred to a unit specialized in the treatment and control of childhood TB for further history-taking, examination, information and, possibly, treatment of LTB.

BCG immunization was introduced as early as 1921 and is the oldest vaccination still in use. It is presently being used in almost all countries in the world, and is given to infants with a coverage of about 85%. Considering this high vaccine coverage, the global burden of TB appears to be a paradox. As a matter of fact, the majority of children with clinical tuberculosis (also verified by cultures) have been immunized and have a visible scar.

Several immunization studies have been undertaken to evaluate the BCG vaccine. In a recent meta-analysis, the protective efficiency was shown to vary considerably from 12 to 85%. However, there is agreement that BCG-vaccination in children protects against primary complications, such as miliary tuberculosis and meningitis, and that the protective efficiency against these could be as high as 85% (14,15).

Two family members with a syndrome of headache and rash caused by human parvovirus B19

A.C.M. Pereira, R.A.Q. Barros, J.P. Nascimento, S.A. Oliveira.
Brazilian Journal of Infectious Diseases 2001; 5(1): 37–39.

AUTHORS' SUMMARY

We describe two cases of B19 infection in a family presenting different clinical features. A 30-year-old female with a history of headache, malaise, joint pains and rash was seen. Two days before, her 6-year-old son had been admitted to a clinic with fever, headache, petechial rash, abdominal pain, neck stiffness, and Kerning and Brudzinski signs. Cerebrospinal fluid analysis was normal. They completely recovered within one week. Acute and convalescent sera of both patients were positive for specific IgM antibody to B19. Human parvovirus B19 should be considered in the differential diagnosis of aseptic meningitis, particularly during outbreaks of erythema infectiosum.

Case report

Case 1

A previously healthy 30-year-old female was seen at our hospital on December 18th with a 7-day history of headache, malaise, myalgias, joint pains involving her hands, knees and ankles, and a 3-day history of body rash excluding her face. Physical examination revealed a maculopapular rash on the patient's extremities and trunk, and swelling and tenderness of both hands at the proximal interphalangeal joints. Her acute and convalescent phase sera had specific immunoglobulin IgM and IgG antibodies against parvovirus B19 confirmed by using, respectively, an antibody capture enzyme immunoassay (1) and an "in house" enzyme immunoassay using recombinant B19 capsids produced in

insect cells (Sf9) as antigen (2,3). She became completely well in one week.

Case 2

A 6-year-old boy was admitted to a private clinic on December 16th with a one-day history of high fever (40°C), headache, abdominal pain and vomiting. On admission, he was alert and oriented; physical examination revealed slight neck stiffness, Kernig and Brudzinski signs, oropharyngeal erythema, tender occipital lymphadenopathy, and a petechial rash on his trunk and extremities. His peripheral white cell count was $3.7 \times 10^3/\text{mm}^3$, with 11% band cells, 63% segmented cells, and 21% lymphocytes. His platelet count was $325,000/\text{mm}^3$. Cerebrospinal fluid (CSF) analysis showed normal cell count and protein

and glucose concentrations. Gram's stained smear, latex agglutination for *Neisseria meningitidis* (Groups A, B, C, YW135), *Streptococcus pneumoniae*, *Streptococcus "B"*, *Escherichia coli* (K1), and culture of CSF were negative. Serum samples from acute and convalescent phases were positive for IgM antibodies to parvovirus B19. Radiography of the facial sinus and chest did not show any abnormalities. Other investigations, including detection of IgM for measles, rubella and dengue, were negative for both patients. A 2-day course of treatment with intravenous ceftriaxone was started for 7 days because of the clinical hypothesis of meningococcal disease. The clinical signs of meningitis and fever completely disappeared in 2 days. However, the petechial rash remained for 3 more days.

Discussion

Despite major advances in pediatric intensive care, meningococemia remains an important cause of morbidity and mortality in Brazilian children. Because the outcome of the disease depends on rapid diagnosis and immediate institution of antibiotics, the diagnosis of meningococemia is best made clinically (4).

Bacterial meningitis is diagnosed in a patient with clinical evidence of meningeal irritation and inflammatory response to infection in the CSF (5). However, confirmation of the clinical diagnosis may sometimes be difficult as bacterial meningitis with normal CSF has been reported by several authors (4–7). Since, at the time of hospital admission, the clinical manifestations of patient 2 were considered to be suggestive of meningococcal infection, he received early treatment with antibiotics. As the child made a rapid uneventful recovery, no other lumbar puncture was done.

The suspicion that both patients were suffering from the same disease was highly suggestive, and was confirmed by the detection of anti-B19 IgM in sera

of both cases. The occurrence of the diseases at the same time, the CSF results, and the prompt recovery of the boy were important clues to consider a viral etiology for both patients.

In immunocompetent individuals, IgM antibody to B19 appears about 10 to 14 days after infection. IgG antibody also appears about two weeks after infection (8). The 6-year-old boy failed to mount an IgG response during the period evaluated. The early collection of the samples might explain this result. However, it was not possible to collect another specimen to detect or demonstrate a rise in B19-specific IgG antibodies.

Central nervous system involvement by parvovirus B19 is rare, and there have been only a few reports of encephalopathy and meningitis (9–12). Our patient presented two unusual clinical manifestations of parvovirus B19 infection: meningitis and petechial rash (13). This case demonstrates that this infection should be considered in the differential diagnosis of patients with aseptic meningitis, particularly during outbreaks of erythema infectiosum. The disease may mimic meningococemia and bacterial meningitis.

Acknowledgements

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EDITORIAL BOARD COMMENT

Although central nervous system involvement by parvovirus B19 is rare, infected patients may present with clinical signs of meningeal irritation and petechial rash. Parvovirus B19 infection should be considered as one of several differential diagnoses in patients with meningitis symptoms and normal findings in cerebrospinal fluid.

Respiratory syncytial virus presenting with status epilepticus

Y.T. Ng, I.J. Butler.
J Child Neurol 2001; 16: 105–108.

AUTHORS' SUMMARY

A 15-month-old girl presented in status epilepticus following a three-day history of upper respiratory tract symptoms. All subsequent investigations were negative, except for positive respiratory syncytial virus testing. In a study of 487 patients presenting with respiratory syncytial virus infection (mainly bronchiolitis), 12 (2.5%) had significant neurological complications, most with prolonged, new-onset seizures. We believe neurological complications to be not uncommon with respiratory syncytial virus infections, and physicians and caregivers alike should be aware of such complications.

Case Report

A 15-month-old Caucasian female with a history of failure to thrive, gastroesophageal reflux and developmental delay presented with a generalized tonic-clonic seizure that persisted for one hour (status epilepticus). She had no previous history or family history of seizures. During the preceding three days, she had had symptoms of rhinorrhea, non-productive cough and fever. Her perinatal history was unremarkable; she was delivered at term, weighing five pounds seven ounces, via normal vaginal delivery. She was microcephalic (head circumference was 43 cm, below the third percentile), but had no focal neurological findings. There was evidence of upper respiratory tract infection, including a red tympanic membrane, but she was not in respiratory

distress. Her temperature was 101.7°F.

Nasopharyngeal aspirate was positive for respiratory syncytial virus (RSV) both on the enzyme-linked immunosorbent assay (ELISA) test and on culture. Other investigations, which were all normal/negative, included computerized tomography and magnetic resonance imaging (MRI) of the brain, electroencephalogram and cerebrospinal fluid analysis (zero cells, with protein and glucose levels in the normal range) and culture. The patient went on to make a good recovery to her baseline and was discharged home.

Discussion

This patient presented with status epilepticus as a significant neurological complication caused by RSV. An extensive work-up was done to exclude other

causes. Despite her dramatic presentation, she went on to make an uncomplicated, complete recovery.

Encephalopathy in association with RSV infection has not been systematically studied. We recently reported on a study of 487 pediatric patients (average age, 32.8 weeks) with RSV bronchiolitis, of whom nine patients (1.8%) had new-onset seizures (two with status epilepticus) (1). Most of the patients with seizures had either prolonged or recurrent seizures (partial and generalized). Many of these patients were under six months of age.

A total of 12 patients (2.5%) were identified with neurological complications. Two of these three patients had a significant hypotonia which was prominent and persistent for several days, prompting nerve conduction studies and electromyography in one patient (whose result was normal). The third patient had transient loss of developmental milestones, acutely for several weeks, following RSV bronchiolitis, with eventual improvement to baseline. The remaining nine patients had seizures that were not simple febrile seizures (1).

Table 1, summarizes the clinical profile of the encephalopathic patients. Table 2, highlights the major investigations performed and the subsequent results on these patients. The case report is patient 2 in both tables.

In trying to identify the child with RSV bronchiolitis who is at risk of developing neurological complications, the cohort of encephalopathic patients was analyzed and compared to all the children with RSV bronchiolitis. No definitive risk factors were identified. Neither age, a history of prematurity nor respiratory disease severity was a predictor for neurological complications. Long-term follow-up has not been done on these patients although, anecdotally, most of them have made a good recovery.

RSV is a common etiologic agent of childhood respiratory infections worldwide and a significant cause of morbidity and mortality. RSV is the chief cause

of hospitalization for respiratory tract illnesses in young children (2). It has been estimated that every year 100,000 children are hospitalized and 2000 children die in the United States due to RSV infection (3). The magnitude of the financial burden of RSV infection is also very large, with an estimated annual cost of \$300 million in the United States (2).

Primary RSV infections are rarely asymptomatic (2). Recent studies have shown that RSV can cause disruption of neural control mechanisms and neural pathways in animals. These changes include reduced, nonadrenergic noncholinergic inhibitory responses and abnormal cholinergic mechanisms (4–6). Thus, whether by direct or indirect inflammatory processes, RSV may have a specific neurotoxic effect and cause an encephalopathy during acute respiratory tract infections.

Apnea is a well-recognized complication among patients with RSV bronchiolitis, particularly in infants and premature babies. An associated encephalopathy, usually seizures, appears to be much less recognized. We believe seizures are not an uncommon compli-

cation, and our original study (1) may be an underestimate as we have continued to observe and treat a number of children with seizures and RSV infection since our study was completed (7). Similarly, several other pediatricians and pediatric neurologists have notified us, anecdotally, of RSV-associated encephalopathies in their patients. In infants and children presenting with seizures or unexplained encephalopathy associated with respiratory symptoms, physicians and other health caregivers should consider RSV infection and obtain appropriate investigations.

Further studies need to be performed to evaluate the incidence and exact nature of encephalopathy associated with RSV infection. With improved awareness and understanding of neurological complications of RSV, more invasive and expensive investigations, e.g., MRI and lumbar puncture, may not be necessary in such RSV-affected patients, and only supportive therapy and reassurance required. Nevertheless, there remains a need for safer and more effective vaccination and therapy (7).

EDITORIAL BOARD COMMENT

Respiratory syncytial virus (RSV) may have a specific neurotoxic effect, and RSV infection is sometimes associated with neurological symptoms. These complications may be more common than previously thought. At the moment, there is no method for identifying children at risk of this encephalopathy, but an increased awareness of the association between RSV and seizures or hypotonia is needed in order to make the correct diagnosis and avoid extensive investigations for various other neurological conditions.

Table 1. Clinical profile of the encephalopathic RSV patients

Patient	Age (months)	Sex	Past history	Presenting complaint	Neurological complication	Other
1	2	M	—	cough, wheeze, fever	generalized seizure	—
2	15	F	SGA, GERD, FTT dev. delay	cough, rhinorrhea, fever	status epilepticus (1 hour generalized tonic-clonic seizure)	—
3	4	M	27-week premature twin NEC, RDS	apnea	few partial seizures	—
4	4	M	—	rhinorrhea, congestion, wheezing	partial → generalized seizure	—
5	1.5	M	VSD	cough, tachypnea, wheezing	generalized seizure	—
6	2	F	31-week premature twin	resp. distress, lethargy, very ill	transient oxygen desaturations and hypotonia with EEG abnormalities	ventilated for 11 days
7	6	F	—	cough, rhinorrhea, fever	status epilepticus (three generalized tonic-clonic seizures)	—
8	2	M	—	resp. distress, vomiting, diarrhea, seizure	two generalized seizures	ventilated for 1 day hyponatremia
9	23	M	28-week premature RDS, GERD, Colitis	resp. distress, cough, rhinorrhea	two generalized seizures	—
10	3	F	Mild jaundice	resp. distress	transient loss of developmental milestones, FTT	—
11	3	F	35-week premature	resp. distress cough	transient hypotonia	ventilated for 4 days
12	12	F	—	fever, generalized seizure	generalized seizure	—

— = none significant; SGA = small for gestational age; GERD = gastro-esophageal reflux disease; FTT = failure to thrive; NEC = necrotizing enterocolitis; RDS = respiratory distress syndrome; VSD = ventricular septal defect.

Table 2. Significant Investigations of RSV patients with encephalopathy

Patient	RSV IF	RSV Culture	CSF	Blood, CSF Cultures	CT Brain	MRI Brain	EEG
1	+	+	N	—	N	N	bilateral, sharp wave discharges
2	+	—	N	—	N	N	N
3	+	+	N	—	N	N	EEG1. multiple epileptiform discharges. EEG2. persistent but improving discharges
4	+	+	N	—	N	N	N
5	+	+	N	—	N	N	EEG1. right hemisphere seizure and slowing. EEG2. right hemisphere epileptiform discharges
6	+	+	T	—	ND	N	EEG1. diffuse multifocal epileptiform discharges. EEG2. multiple epileptiform discharges. EEG3. improved, nearly normal
7	+	+	N	—	ND	ND	N
8	+	—	N	—	N	ND	generalized slowing and spike discharges
9	+	+	ND	ND	ND	ND	N
10	+	—	ND	ND	ND	ND	ND
11	+	—	ND	ND	ND	ND	(EMG/NCS = N)
12	+	+	N	—	ND	ND	N

IF = immunofluorescence; CSF = cerebrospinal fluid; + = positive; — = negative; N = normal; ND = not done; T = traumatic; EMG = electromyography; NCS = nerve conduction studies.

Utility of Wang needle aspiration in the diagnosis of actinomycosis

I. Bakhtawar, R.F. Schaefer, N. Salian.
Chest 2001; 119(6): 1966–8.
Reprinted with permission from Chest.

AUTHORS' SUMMARY

We report a patient with a 4-year history of recurrent pneumonia with persistent pleural effusions who underwent repeated bronchoscopy with biopsies of a right bronchus intermedius mass and bronchial washes which remained non-diagnostic. A repeat bronchoscopy and a Wang needle aspiration of the mass was obtained which showed sulfur granules, diagnostic of actinomycosis. Actinomycosis should be considered in the differential diagnosis of recurrent pneumonia and an endobronchial mass. Wang needle aspiration per bronchoscopy may be an important diagnostic tool.

Case report

An 85-year-old African American male was admitted in August 1999 with a one-day history of nausea, vomiting and left flank pain. He also reported mild shortness of breath at rest, off and on for the past 4 years. Since February 1996, he has had recurrent episodes of pneumonias and persistent bilateral pleural effusions. An extensive workup included a computerized tomography scan of the chest showing right middle and right lower lobe atelectasis with bilateral pleural effusion, and calcified lymph nodes in the pre-carinal and right hilar area. Repeat bronchoscopy done over time revealed a right bronchus intermediates (RBI) mass occluding 90% of its orifice. However, sputum obtained, mucosal biopsies of the mass and wash collected from the right bronchus inter-

medius, multiple thoracentesis, and a pleural biopsy have all proved to be non-diagnostic.

His past medical history was significant for a tooth abscess in February 1996, preceding his initial pneumonia; diabetes mellitus type II; hypertension; atrial fibrillation; chronic renal insufficiency; 30-pack per year history of smoking, now an ex-smoker; and a history of moderate alcohol use. On physical examination, the patient was in mild respiratory distress. Lungs had percussion dullness in the right base, with decreased air entry on auscultation and decreased tactile fremitus. His pulse was irregularly irregular. Abdominal palpation elicited mild tenderness over the left costovertebral angle and left lower quadrant. Edema was noted on the lower extremities.

Laboratory analysis revealed a urinary tract infection and a low hemoglobin. Chest x-ray showed increased right pleural effusion compared to June 1999. A computerized tomography scan of the chest done 3 weeks prior to admission showed interval increase in right-sided pleural effusion and non-visualization of a short segment of the bronchus intermedius. Bronchoscopy was repeated, and the mass obstructing the right bronchus intermedius was seen again (Figure 1). Wash was collected from the right bronchus intermedius, and Wang needle aspiration of the mass was obtained. The Wang needle aspirate revealed colonies of *Actinomyces* with sulfa granules (Figure 2). He was given intravenous ceftriaxone for 4 weeks to be switched to amoxicillin for an additional 5 months.

Discussion

Actinomycosis is a chronic suppurative bacterial infection. The causative agents are Gram-positive, non-spore forming anaerobic or microaerophilic rods. They are endogenous oral saprophytes which dwell in carious teeth, dental plaque, and gingival and tonsillar crypts (1). Pulmonary actinomycosis is mainly acquired through aspiration of organisms from the oropharynx (1). The history of the tooth abscess in our patient could be relevant. Thoracic involvement is seen in 15 to 20% of actinomycosis cases. It classically presents as either a mass lesion or pneumonitis with or without pleural involvement. Primary endobronchial actinomycosis is an exceptionally uncommon presentation of the disease, as seen in our case.

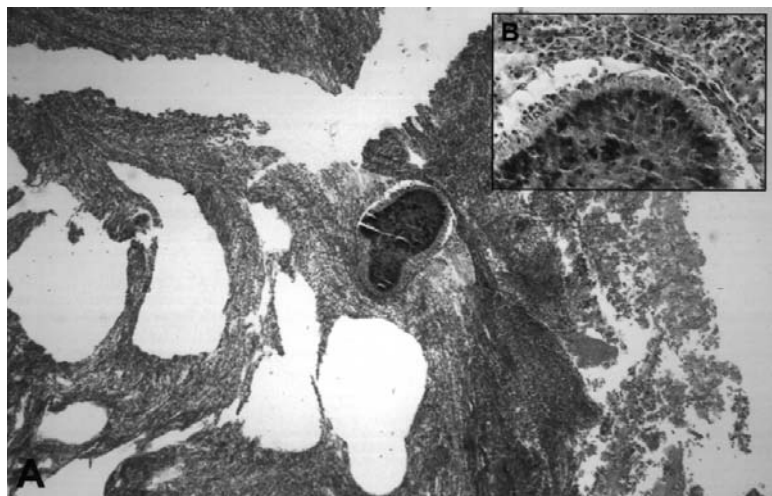
The hallmark of actinomycosis is the formation of yellow sulfur granules. Although they may be abundant, only a single granule was identified in 26% of specimens in one series (2). Actinomycosis can be found in 30 to 50% of normal saliva specimens (3), so a diagnosis cannot be made from sputum cytology and/or culture unless the specimen is obtained directly from the

Figure 1.



Bronchoscopy picture: bronchoscope in the right main stem bronchus showing the endobronchial mass occluding the right bronchus intermedius and a patent upper lobe bronchus.

Figure 2.



Fine needle aspirate: A) Magnification x 40, H and E section reveals a granule of actinomycosis surrounded by an intense reaction of leukocytes; B) Magnification x 450, higher magnification of the organized aggregate of filamentous bacteria forming a spherule with an eosinophilic rim representing the Splendore-Hoeppli phenomena.

bronchus. The organism grows in anaerobic culture medium; the bronchial wash collected in our case was cultured under aerobic conditions only and was negative. In the past, thoracotomy was the procedure of choice for the diagnosis of *Actinomyces* (4,5). Fibro-optic bronchoscopy has allowed a minimally invasive approach to make the diagnosis. However, the diagnostic yield has been low on bronchoalveolar lavage, bronchial wash and bronchial biopsies reported (4,6). It has been reported that physiological saline, which is commonly used for bronchoalveolar lavage, inhibits the growth of pathogenic *Actinomyces* (7). It can be speculated that in a small crushed bronchial biopsy the morphologic appearance of the sulfur granule may get distorted, making diagnosis difficult. The Wang needle aspirate allowed collection of a sub-mucosal tissue sample unlike the mucosal biopsies, showing the sulfur granules, diagnosing actinomycosis.

Review of the literature over the past 25 years has revealed no reported case of endobronchial actinomycosis diagnosed with a Wang needle aspiration. A delayed diagnosis up to 44 months from the beginning of symptoms is reported by all authors (4), as also observed in our patient. Endobronchial actinomycosis should be considered in the differential diagnosis of recurrent pneumonia with an endobronchial mass. Fiberoptic bronchoscopy could help avoid a surgical procedure and aid in making a diagnosis. Wang needle aspirate per bronchoscopy may be used to obtain clinical material for diagnosis.

EDITORIAL BOARD COMMENT

Actinomycosis is a forgotten pathogen in recurrent episodes of pneumonia. Several lessons can be learned from this case report. First, it should be remembered that sputum cultures are not sufficient, since the pathogen can be found in 30–50% of normal saliva specimens. Secondly, *Actinomyces* grows only under anaerobic conditions and can therefore be missed if anaerobic cultures are not taken. Lastly, bronchoalveolar lavage, where physiological saline is used, may inhibit the growth of *Actinomyces*.

Left atrial myxoma with endocarditis

P. Dekkers, W. Jaarsma.

Journal of the American Society of Echocardiography 2001; 14(6): 644–5.

AUTHORS' SUMMARY

A 40-year-old male presented with fever, malaise and weight loss. A blood culture was positive for *Streptococcus mutans*. Under the suspicion of endocarditis, he was treated with penicillin. Echocardiography revealed a large tumor in the left atrium. After six weeks of treatment, the tumor was excised. Pathology revealed a myxoma with fibrin deposits, bacterial colonization and massive infiltration with neutrophils.

Case report

A 40-year-old male presented with a 16-day history of fever. He also had malaise, fatigue, dyspnea and a 5 kg weight loss in 5 months. There was no history of recent surgical or dental interventions or drug abuse. He had been treated with doxycycline for 2 weeks by his general physician without success. A blood culture was positive for *Streptococcus mutans*. Under the suspicion of endocarditis, he was admitted to a local hospital for further treatment with intravenous penicillin. Physical examination showed a body temperature of 37.4°C and normal heart sounds without murmurs or signs of heart failure. Further examination showed no abnormalities. Laboratory studies showed an erythrocyte sedimentation rate of 37 mm/h and a white blood cell count of $16 \times 10^3 / \text{mm}^3$. CRP was 39 mg/L. Chest

radiography was normal. Transthoracic echocardiography and transesophageal echocardiography revealed a large tumor in the left atrium which was inserted in the atrial septum. The tumor did not show a smooth round appearance, normal for a myxoma, but showed a ragged edge and thin, finger-like mobile structures consistent with vegetations. There were no valve abnormalities, and there was normal function of both the ventricles (Figure 1, page 18).

After 6 weeks of treatment, body temperature, erythrocyte sedimentation rate and CRP returned to normal values. He was then transferred to our hospital for surgical removal of the tumor. He recovered without complications and was discharged 8 days after surgery. Pathology revealed a typical cardiac myxoma with hemorrhage and calcifications (Figure 2, page 18). Further-

more, a diagnosis of bacterial endocarditis was made on the basis of the presence of fibrin deposits with bacterial colonization and massive infiltration with neutrophils. Cultures of the myxoma were negative.

Discussion

Although the most common cardiac tumor, myxoma is a rare entity and seldom becomes infected (1–6). Infected and uninfected myxomas may exhibit the same symptoms, such as fever, weight loss, fatigue and malaise, making the correct diagnosis difficult. In a review article, Revankar and Clark (4) stated that only fever and elevated sedimentation rate were significantly more frequent in patients with infected myxomas than those with uninfected myxomas. This patient did not have a tumor with the smooth edges normally found in an uninfected myxoma. Instead, transesophageal echocardiography showed a tumor with a ragged edge and thin mobile structures consistent with vegetations. Although there are, to our knowledge, only two earlier case reports that describe an infected myxoma found by transesophageal echocardiography, transesophageal echocardiography is the most logical method for demonstrating vegetations, such as those observed in endocarditis of the valves (5,7). We conclude that an infected myxoma must be considered when a patient has fever and an elevated sedimentation rate. An infected myxoma is likely when blood cultures are positive and transesophageal echocardiography shows vegetations on the myxoma or proof of additional sites of infection, such as valve endocarditis or perivalvular abscess. Little is known about the correct strategy for treatment of an infected myxoma (3–6,8). Unlike the experience with this patient, we advise prompt surgery in combination with proper antibiotic treatment to minimize the risk of embolization or valve involvement.

Figure 1.

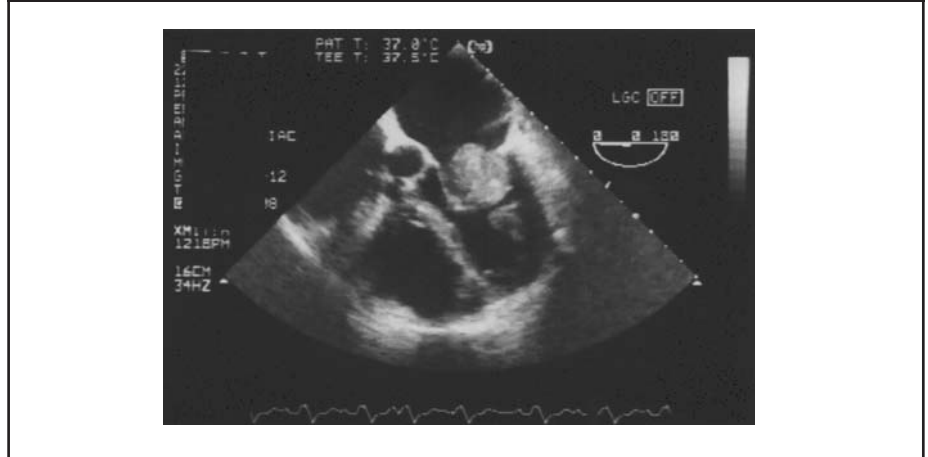
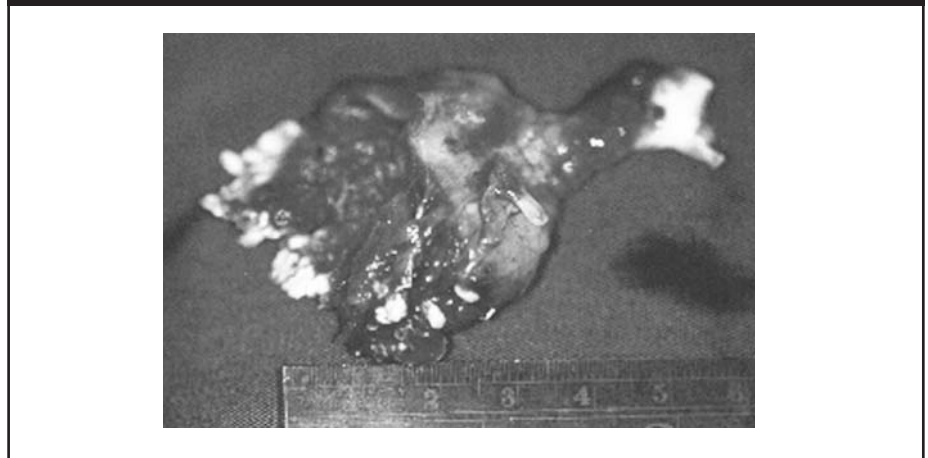


Figure 2.



EDITORIAL BOARD COMMENT

This case report concerns a patient with a history of fever, malaise and weight loss. A blood culture showed *Streptococcus mutans*. In such a patient, endocarditis must be suspected and antibiotic treatment should be initiated. Transesophageal echocardiography should be performed as soon as possible. The examination revealed a tumor in the left atrium. The combination of such a tumor and endocarditis is uncommon. Adequate antibiotic treatment and early contact with the surgical department are recommended.

Native aortic valve tissue systemic embolization complicating bacterial endocarditis

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Clinical Cardiology 2001; 24: 166–168.

AUTHORS' SUMMARY

Systemic embolization is a common complication of infective endocarditis. Embolization of prosthetic valves has previously been reported in the literature. We report a case of embolization of native aortic valve tissue to the popliteal artery resulting in severe aortic regurgitation. The patient underwent embolectomy and subsequently required aortic valve replacement. Pathological review of the extracted embolus revealed the presence of valvular tissue within it. To our knowledge, this rare complication has not been previously reported.

Case Report

A 41-year-old Caucasian woman with no prior cardiac history was admitted to our hospital with a history of left calf pain of three days duration. She also reported fever chills and malaise for the 3 days prior to admission. She had a remote history of intravenous drug use, and denied intravenous drug use for over 10 years. On examination she was febrile (100.2°F), her pulse was 92 beats per minute regular, and her blood pressure was 150/60 mmHg with peripheral signs of widened pulse pressure. Pulses in the left foot were absent but normal on the right. Cardiac examination revealed hyperdynamic, laterally displaced, diffuse point of maximal impulse. A grade III/VI systolic ejection murmur was audible at the right upper sternal border and an early diastolic murmur was audible over the left sternal

border, consistent with the presence of significant aortic regurgitation. An arterial Doppler study of the left lower extremities was consistent with thrombotic occlusion of left popliteal artery. Transthoracic echocardiogram on admission revealed severe aortic regurgitation. The aortic valve itself was poorly visualized.

Urgent surgical thromboembolectomy successfully revascularized the leg, and the patient's postoperative course was unremarkable. Transesophageal echocardiogram performed 2 days later showed thickening at the tips of the right and left coronary cusp leaflets of the aortic valve with destruction of the noncoronary cusp. The distal half of the noncoronary cusp was completely missing (Figure 1, page 20), resulting in torrential aortic regurgitation. The other valves were normal and no additional

vegetations were noted. The left ventricle was mildly dilated (left ventricular end-systolic diameter, 4.6 cm) with preserved systolic function (ejection fraction, 50–55%).

Pathologic review of the extracted thrombus revealed the presence of valvular tissue within the thrombus (Figures 2A and 2B, page 21). Blood cultures and popliteal thrombus cultures were positive for *Streptococcus sanguis* (*Streptococcus viridans* group). The patient was treated with 2 gm/day of intravenous ceftriaxone for 4 weeks. Prior to undergoing the planned aortic valve replacement, she was admitted to the hospital with symptoms of increasing shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea.

Physical examination was consistent with signs of congestive heart failure. Transthoracic echocardiogram showed persistent severe aortic regurgitation with further dilatation of the left ventricle (left ventricular end-systolic diameter, 5.3 cm) and worsening systolic function (ejection fraction approximately 35% compared with 50–55% six weeks previously). No vegetations were visualized. Blood cultures were sterile. The patient was referred for emergent aortic valve replacement, and a St. Jude no 23 prosthetic aortic valve was placed. The patient did well postoperatively, and repeat echocardiogram done 6 weeks postoperatively showed a normally functioning prosthetic aortic valve, and unchanged left ventricular systolic function (EF approximately 35%). The left ventricular end-systolic diameter had decreased to 3.6 cm (from 5.3 cm preoperatively).

Discussion

Infective endocarditis is associated with both symptomatic and asymptomatic systemic embolization that can variably influence prognosis (1–7). Lower extremity arterial embolization has been described in infective endocarditis with an incidence as high as approximately 3% in one series (8). Heart valve embolization

has been reported for both mechanical (8–12) and biological (13,14) prosthetic heart valves as a rare but serious complication. Prosthetic valve embolization usually results in death (8–9,13) or permanent sequelae (10,11). Emergent surgery is usually indicated and may be successful (12). There are few data on native valve embolization. Our patient had embolization of native valve tissue to the popliteal artery as a consequence of severe destructive endo-

carditis. This, in turn, resulted in severe aortic regurgitation. Although this patient did not present with severe LV dysfunction due to the acute development of severe aortic valve insufficiency, the progressive worsening of LV function, and the need for early surgery suggests that such patients be followed closely and perhaps be referred for surgery earlier in the course of antibiotic therapy (i.e., before completion of the entire course of treatment).

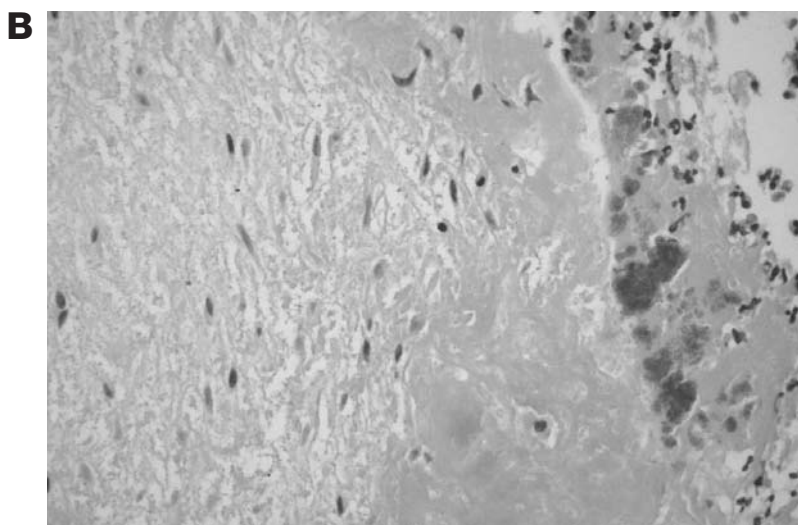
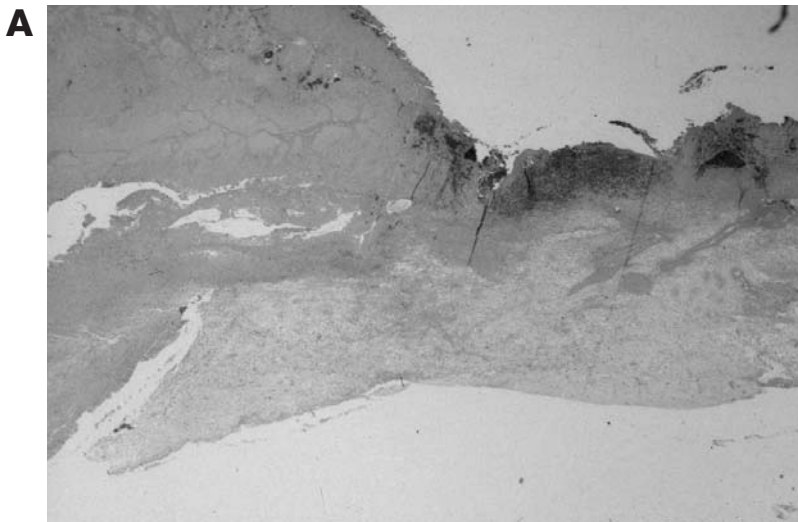
Figure 1.



Transesophageal echocardiogram view of the aortic valve demonstrating missing of a portion of the noncoronary cusp of the aortic valve

EDITORIAL BOARD COMMENT

Bacterial endocarditis is a serious disease with different complications. This patient presented with fever and systolic ejection murmur, and she also had an embolization of the popliteal artery. Embolization has been described for both mechanical and biological heart valves. The event in this patient is very rare since it comes from the native aortic valves. Transesophageal echocardiography should always be performed as soon as possible in such a patient. Adequate antibiotic treatment and early contact with the surgical department are recommended.

Figure 2.

(A) Low power view of valve tissue showing adherent fibrin thrombus with bacterial colonies. Hematoxylin and eosin stain, 130 x magnification.

(B) High power view of valvular tissue showing degenerative changes, adherent thrombus with valvular colonies and acute inflammatory cells. Hematoxylin and eosin stain,

***Candida tropicalis* and *Penicillium marneffe* mixed fungemia in a patient with Waldenström's macroglobulinemia**

S.S.Y. Wong, P.C.Y. Woo, K.Y. Yuen.

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AUTHORS' SUMMARY

A patient with Waldenström's macroglobulinemia was previously treated with the purine nucleoside analogue, cladribine. Following an episode of *Escherichia coli* infective arthritis, the patient developed profound lymphopenia which was complicated by mixed fungemia due to *Candida tropicalis* and *Penicillium marneffe*. Mixed fungemia in patients suffering from *Penicillium marneffe* infection had not been reported previously. *Penicillium marneffe* is an important opportunistic fungal infection in Southeast Asia, predominantly among patients infected by the human immunodeficiency virus (HIV). Nevertheless, infections in non-HIV-infected patients have also been reported and should be considered a potential pathogen in patients with cellular immune defects in endemic areas.

Case report

A 73-year-old Chinese man was diagnosed to be suffering from Waldenström's macroglobulinemia (WM) since 1990, the last course of which was completed in 1996 with the use of cladribine. He required regular erythrocyte transfusion but was otherwise asymptomatic. In February 1999, he developed an episode of left knee arthritis. Culture of the joint fluid yielded a pure growth of *Escherichia coli*. He was initially treated with intravenous cefuroxime followed by oral cefuroxime axetil maintenance.

Forty days after the initial admission for septic arthritis, he was readmitted for persistent left knee arthritis. Joint fluid culture yielded the same strain of

Escherichia coli, and the patient was treated with intravenous ceftriaxone and gentamicin. Clinically, the arthritis was improving with the antibiotic regimen, but the patient developed an episode of *Clostridium difficile*-associated diarrhea (confirmed by a positive culture and cytotoxin assay in stool) which was controlled by a course of oral metronidazole.

He remained afebrile until day 19 when he developed fever up to 38.8°C. His clinical condition subsequently deteriorated, with dyspnoea, tachycardia, hypoxemia, worsening right basal pulmonary consolidation, and mental obtundation. Blood culture taken on day 40 was positive after 24 h of incubation for a yeast, subsequently identified as

Candida tropicalis. Intravenous fluconazole was started on day 41. On day 49, another set of blood culture samples, also taken on day 40, was found to be culture-positive for a mould in addition to *Candida tropicalis*. The mould demonstrated thermal dimorphism, i.e., when cultured on Sabouraud agar at 25°C, the colonies were mycelial in nature, greenish yellow in colour, and produced a diffusible red pigment. Microscopically, the mycelia bear numerous penicilli, as seen in other *Penicillium* species. When cultured at 37°C, yeast-like colonies were formed without pigment production. The mould was identified as *Penicillium marneffeii*, and the organism was also isolated from the endotracheal aspirate of the patient taken on the same day. Fluconazole was switched to intravenous amphotericin B, but the patient subsequently succumbed on the following day. The patient had profound lymphopenia (total lymphocyte count 0.1 to 0.3 × 10⁶/mL) during the latter stage of the illness.

Discussion

Penicillium marneffeii is a dimorphic fungus endemic in Southeast Asia. Cell-mediated immunity is most crucial in determining the susceptibility to disease. The majority of patients are HIV-infected, up to 90% in some series (1). Non-HIV patients are usually immunocompromised, such as those with hematological malignancies and autoimmune diseases requiring corticosteroid therapy (2,3).

WM is a low-grade lymphoplasmacytic lymphoma characterized by monoclonal IgM gammopathy due to uncon-

trolled proliferation of lymphocytes and plasma cells (4). The nucleoside analogues are effective agents against malignancies of lymphoid origin. Cladribine is highly toxic towards both proliferating and resting lymphocytes and has been used for the treatment of hematological malignancies, including hairy cell leukemia, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, and WM (5). The toxicity towards lymphocytes accounts for some of the infective complications following cladribine therapy: most of the reported pathogens are classically associated with impaired cell-mediated immunity, such as *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Mycobacterium avium-intracellulare*, *Listeria monocytogenes*, and *Pneumocystis carinii* (6–13). The most significant immunological abnormality present at the time of *Penicillium marneffeii* fungemia in this reported case was profound lymphopenia. This could be a result of multiple factors, including previous cladribine treatment, prolonged illness due to infective arthritis, as well as malnutrition. Reactivation of latent infection is the most likely source of fungemia in this patient. Latent infection is evidenced in other case reports by the late reactivation of the disease in patients who had long left endemic areas. It is therefore possible that, in the face of a waning cellular immunity, *Penicillium marneffeii* could reactivate, as occurs with other pathogens, such as *Mycobacterium tuberculosis*.

A recent report compared the differences in the clinical and laboratory manifestations of *Penicilliosis marneffeii* among HIV-infected and non-HIV-

infected patients in Hong Kong (14). Non-HIV-infected patients commonly have hematological malignancies, autoimmune diseases, and diabetes as the predisposing conditions. The HIV-infected subjects were more likely to have fungemia at the time of diagnosis. More importantly, the delay in the time of diagnosis from initial presentation is significantly longer in the non-HIV infected patients, presumably due to more atypical presentations or lack of awareness by the clinicians. Using an ELISA antigen and antibody assay based on a recombinant *Penicillium marneffeii* cell wall antigen Mp1p (15), the HIV-infected patients tended to have a higher serum antigen and lower antibody titer than the HIV-negative patients.

The diagnosis of penicilliosis marneffeii is problematic, as in other systemic fungal infections; in most cases, this still relies on conventional fungal culture and histopathology of suspicious lesions. Although fungemia is relatively common in HIV-infected patients, this may not be the case in non-HIV-infected patients who may have a lower fungal load. The need for prolonged incubation of the blood culture is the main limitation in most situations. In this case of mixed fungemia with *Candida tropicalis*, *Penicillium marneffeii* may initially be missed owing to a slower growth rate than *Candida*. This could adversely affect the efficacy of treatment because fluconazole, which is commonly used for the empirical therapy of fungemia in non-neutropenic patients, is not the treatment of choice for penicilliosis marneffeii (16). Amphotericin B and

itraconazole are the mainstays of therapy. Standard antifungal regimen consists of two weeks of intravenous amphotericin B, 0.6 mg/kg/day, followed by oral itraconazole, 200 mg bid, for 10 weeks (17). There are no controlled trials on the optimal therapy of penicilliosis marneffei in non-HIV-infected patients. An initial course of intravenous amphotericin B, especially in the compromised hosts, is usually given followed by itraconazole maintenance therapy when the condition improves.

Penicilliosis marneffei should therefore be considered as an opportunistic infection in endemic areas among patients with significantly impaired cell-mediated immunity due to underlying diseases or chemotherapy with agents such as corticosteroids or nucleoside analogues. Mixed infection with other fungi is rare, but may potentially delay the initiation of effective antifungal therapy.

EDITORIAL BOARD COMMENT

Penicillium marneffii is an important opportunistic fungal pathogen in South-East Asia, and it has received widespread attention with the HIV epidemic. However, it may also appear in HIV-negative patients with other cellular immune defects, as illustrated by this case of a lymphopenic man with cladribine-treated Waldenström's macroglobulinaemia. Furthermore, the case illustrates that *Penicillium marneffei* can occur as a mixed fungemia with *Candida*. Diagnosis may be delayed, resulting in a choice of inappropriate treatments since the growth rate of *Candida* in blood cultures is higher than that of *Penicillium*.

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Two family members with a syndrome of headache and rash caused by human parvovirus B19

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