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Management of fever in returning travellers

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Fever is a common manifestation of many illnesses acquired during travel. Accurate diagnosis requires a systemic approach to obtain the vital information in the swiftest manner so that appropriate treatment can be given. A delay in diagnosis is often quoted as one of the major contributing factors for adverse outcome in certain conditions like malaria.

Knowledge of likely etiology of fever

Fever can either be infectious or non-infectious in origin. Depending on destination of travel, the infection can either be tropical or non-tropical. Common tropical infections include malaria, typhoid, hepatitis and dengue fever. Pulmonary embolism and drug fever are important non-infectious conditions to consider. One should also note that non-infective causes for pyrexia of unknown origin like malignancy and connective tissue diseases may as well occur in travellers.

Most febrile illnesses in travellers are self-limiting and requires only symptomatic treatment, examples of which include acute viral upper respiratory tract infection and travellers' diarrhoea. On the other hand, some "exotic" infections may pose diagnostic challenge to clinicians because of unfamiliarity with the epidemiology and clinical features of these conditions. The aim of management would be detection of serious treatable or communicable infections while not submitting the majority of travellers with benign, self-limiting causes of fever to expensive or invasive diagnostic evaluation.

Accurate travel history

People nowadays travel to a wide variety of geographical locations for pleasure, business or other purposes. Most destinations on earth can be reached within 36 hours which is less than the incubation period of most infections.

It is essential to obtain an accurate travel history covering potential risks of exposure to specific infections. The exact routing, purpose of travel and accommodation should be inquired. Even when travelling within the same country, the exposure risk to disease vectors and unclean food is obviously greater for say an adventurous backpacker exploring the jungle than for a businessman staying mostly indoor in a luxurious hotel during the trip. Details of pre-travel vaccination may help to narrow down the differential diagnosis but protection is not absolute in most infections e.g. typhoid vaccines are at best 70% protective. The use of anti-malarial prophylaxis does not rule out the possibility of malaria as the underlying cause of the presenting fever, especially if the prophylaxis used is inappropriate for the region concerned or if the patient is only partially compliant.

Besides ingestion of unclean food or water, which may be associated with enteric infections and hepatitis A and E, other more specific exposure history can sometimes give important clue to diagnosis. Examples include acquisition of schistosomiasis and leptospirosis after fresh water swimming or sports, acquisition of malaria and dengue fever after mosquito bites and acquisition of rabies and Q fever after animal exposures. People tend to loosen up during travel hence the importance of asking about sexual exposure tactfully. Acute human immunodeficiency virus (HIV) seroconversion may present with an acute "mononucleosis-like syndrome" usually 4 to 6 weeks after exposure. In the same vein, history of misuse of substance and sharing of needles should be inquired when appropriate.

Knowledge of outbreaks and incubation period of infections
With the help of travel history, we may be able to prioritize the differential diagnosis. Knowledge on current disease outbreaks can be obtained easily from resources like the Internet. Unusual infections like plague, diphtheria, Hantavirus and meningococcal infection may have to be considered under appropriate situation.

Most returning travellers will present with fever within the first three weeks of their return. Whereas infections like dengue fever, typhus, leptospirosis, plague and viral haemorrhagic fevers have short incubation period of less than 3 weeks, infections like acute schistosomiasis, tuberculosis, amoebic liver abscess, HIV seroconversion, acute hepatitis have longer incubation period. The incubation period of malaria and typhoid fever can vary between 1 to 4 weeks.

Clinical examination
Fever pattern is generally not useful. "Saddle back" fever (second lower peak of fever) may occur in dengue fever. Typhoid fever is typically continuous and associated with pulse-temperature deficit, though the latter may also occur in conditions like viral infections.

One should inspect the body fully for the presence of rash, which can sometimes be subtle especially in the early stage of disease. Maculopapular rash may be found in dengue, HIV seroconversion, rickettsial infection, acute hepatitis B and leptospirosis. Rose spots in typhoid fever are typically faint and sparse, blanched with pressure and occur mainly on the trunk. The presence of eschar (painless ulcer with a black centre and erythematous margin) should make one consider scrub or tick typhus or rarely cutaneous diphtheria. One should note that eschars are commonly found in unexposed areas like below the undergarment or the axilla, emphasizing the importance of thorough physical examination.

Presence of lymphadenopathy may signal HIV seroconversion, dengue fever, and rickettsial infection. Lymphadenopathy is not a feature of malaria, typhoid and paratyphoid fever.

Splenomegaly may be found in malaria, typhoid fever, rickettsial infection, dengue fever, brucellosis, relapsing fever and a variety of other infections hence its presence is not too useful in narrowing down the differential diagnosis. Hepatomegaly may be found in amoebiasis, malaria, typhoid, viral hepatitis and leptospirosis.

Haemorrhage may be found in conditions like viral haemorrhagic fevers, dengue fever, yellow fever and meningococcal septicaemia.

Investigations
Essential investigations include complete blood count, routine biochemical tests, cultures of blood and urine and a properly done malaria smear. Neutrophilia may be found in bacterial enteritis, amoebiasis, pneumonia and leptospirosis among the many bacterial infections. Leucopenia may be found in arbovirus infection (especially dengue), influenza and typhoid fever. Katayama fever (acute schistosomiasis) and filariasis may be associated with eosinophilia. Thrombocytopenia is common in malaria, viral and rickettsial infections.

Whereas liver function tests are significantly abnormal in acute viral hepatitis; mild to moderate abnormalities are common in malaria, typhoid fever, dengue fever, typhus, HIV seroconversion, brucellosis and in any severe infections.

Blood culture remains the golden standard for diagnosis of typhoid fever and may be positive in pneumonia or urinary tract derived bacteraemia. Stool and urinary culture should be done when appropriate. It may be prudent to save an acute serum sample for future comparative serologic studies.

Specific diagnostic tests should be ordered according to clinical evaluation and initial laboratory investigations e.g. CSF examination in the presence of meningism. Serological tests are available for dengue, rickettsial infection, HIV, viral hepatitis, atypical pneumonia pathogens like mycoplasma and chlamydia, amoeba, and certain parasitic diseases. If intestinal amoebiasis is suspected, fresh stool should be sent for microscopy. Liver abscess may show up as elevation of right hemidiaphragm on chest X-ray.

Management
The exclusion of malaria is a priority. Plasmodium falciparum malaria in a non-immune patient is a medical emergency. Patient should be admitted and given appropriate anti-malarial drugs without delay.

After all is said and done, a proportion of fever may remain undiagnosed. It is then time to review the physical signs and perform further investigations as appropriate. Presumptive empiric therapy directed against a likely pathogen may be justified, especially when adequate diagnostic studies are not readily available or when the patient is clinically deteriorating.

Typhoid and typhus require specific antibiotics for treatment. Most viral infections are treated with supportive measures. Conditions like bacterial enteritis are often self-limiting.

Apart from drug treatment, notification of infection is important for public health reason.

Before ending, it should be noted that most infections acquired during travel may be prevented with proper pre-travel counselling and prophylactic measures.

Useful travel medicine websites
- International Society of Travel Medicine —**http://www.istm.org**
- Armchair World Travel Medicine —**http://www.armchair.com/info/chos.html**
- Travel Health Online —**http://www.tripprep.com/**
- MASTA Travel Advice —**http://www.masta.org/**
- World Health Organization —**http://www.who.ch**
- Centres for Disease Control and Prevention (US) —**http://www.cdc.gov**

Useful telephone numbers
- Port Health Office, Department of Health, Hong Kong:
  2961 8840 (Hong Kong Vaccination Centre)
  2368 3361 (Kowloon Vaccination Centre)
- Travel Clinic, Princess Margaret Hospital: 2990 1586

Norwalk-like viruses

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Background
Norwalk-like viruses (NLVs) have been implicated in up to 40% of outbreaks of non-bacterial gastroenteritis (GE) and are important pathogens in terms of clinical disease and economic costs. NLVs are also known as small round structured viruses (SRSVs) in accordance with their morphology under electron microscopy (EM). The clinical syndrome caused by this group of viruses was first described in 1929 as "winter vomiting disease". The prototype Norwalk virus was first identified by EM in 1972 in stool samples from an elementary school outbreak of GE in Norwalk, Ohio, USA, with significant secondary spread. Since then, numerous similar but genetically distinct viruses collectively known as NLVs have been described, each named after the locale where it was first implicated in an outbreak. NLVs are RNA viruses and are now classified as members of the family *Caliciviridae*. Two major

genogroups are recognised, namely group 1 (including Norwalk, Southampton, Desert Shield, etc.) and group 2 (including Lordsdale, Snow Mountain, Hawaii, etc.). Efforts to enhance understanding of NLVs have so far been hampered by the inability to culture them.

Epidemiology

GE caused by NLVs is an extremely common illness affecting all age groups with a worldwide distribution. Although the disease has initially been known as "winter vomiting disease", many studies have demonstrated no seasonal variation or only a minor preponderance during the cooler months. Humans are the only known reservoir. Two patterns of illness are recognised depending on the source of infection. In the first form, the illness is initially sporadic and acquired through person-to-person transmission via the faecal-oral route, direct contact with infectious materials (e.g. vomitus), indirect contact through fomites, or airborne transmission of infectious droplets. Such sporadic cases have a high degree of secondary spread often resulting in point-source outbreaks, especially in families and institutions such as nurseries and schools. In the second pattern, the occurrence is characteristically epidemic and consists of outbreaks traceable to ingestion of undercooked bivalve shellfish (especially oysters), or food or water contaminated by an infected food-handler or by other means. Such common-source outbreaks have been reported in restaurants, cruise ships, public swimming pools and other settings, again with a high degree of secondary spread.

Clinical features

The infective dose of NLVs causing GE is extremely low. Infection results in mucosal lesions in the proximal small intestine, causing malabsorption. The infection is subclinical in some cases. In others, after an incubation period of 24 to 48 hours, symptoms may include a combination of nausea, vomiting which is often projectile, non-inflammatory diarrhoea, and abdominal pain of varying degree of severity. Constitutional symptoms such as low-grade fever, malaise, headache and myalgia occur in 25 to 50% of cases. The illness characteristically lasts 24 to 48 hours and the clinical course is usually benign and self-limiting although it can occasionally be severe especially in the immunocompromised and elderly. The disease is usually communicable during the acute stage of illness and up to 48 hours after diarrhoea stops. Short-term immunity lasting up to 14 weeks has been demonstrated in volunteers after induced Norwalk illness, but long-term immunity is variable and re-infection may occur on re-challenge.

Diagnosis

Although clinical and epidemiological features are not distinctive of NLV infection and definitive diagnosis depends on laboratory testing, the disease is mild and self-limiting in most cases and no laboratory investigation is necessary. Diagnostic tests are performed usually when there is public health significance such as during outbreaks and for surveillance. Since the virus is non-cultivable and reagents for antibody testing are not generally available, diagnosis depends largely on direct detection of the virus or its components. Traditionally, EM is the mainstay of diagnosis with the ability to detect other GE viruses as well, such as rotavirus, enteric adenovirus and astrovirus. However, the equipment is expensive and experienced technologists are required. In addition, in order to increase the diagnostic yield, diarrhoeal stool specimens need to be collected early during the symptomatic phase of the illness. Recently, direct detection of viral RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) has been increasingly used and detection of the virus is possible up to 7 days after symptom onset.

Management

Since the disease induced by NLVs is usually mild, oral fluid and electrolyte replacement is sufficient in most cases. If severe vomiting or diarrhoea occurs, hospitalisation and parenteral fluids may be necessary. Antibiotics and antimotility drugs are contraindicated. In experimentally induced Norwalk virus infection, oral bismuth subsalicylate has been shown to decrease the severity and duration of abdominal cramps. Apart from individual patient management, food poisoning is a notifiable disease in Hong Kong. In such cases and also for any outbreak situation, the Department of Health should be informed so that investigations can be carried out to document the nature of the outbreak and determine the source of infection. Advice on hygienic practices and disinfection will also be provided to prevent further spread of the disease.

Prevention

The ultimate source of infection is humans excreting the virus. Sanitary disposal of sewage and hygienic measures such as adequate disinfection of contaminated materials are important to eliminate the source of infection. To prevent transmission of NLVs through ingestion of contaminated food or water, especially undercooked bivalve shellfish, it is essential that the public is educated on the necessity for maintaining food hygiene and the risks associated with eating any food item that is not thoroughly cooked. Education is also required to ensure proper food-handling practices in commercial premises, especially on preparation of food that requires handling and no subsequent cooking. Any food handler with gastroenteritis should defer from work until 48 hours after stopping diarrhoea. Measures to protect oyster beds and better surveillance indicators for oyster quality are also needed to further enhance food safety. Regarding immunisation, since the basis for long-term immunity is still not understood and the virus could not be successfully cultured, this method of prevention is not currently feasible.

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Hand, foot and mouth disease in Hong Kong, 1999

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In 1998, outbreaks of Enterovirus 71 (EV71) infections have occurred in children in Malaysia, Taiwan and Hong Kong. The majority of patients presented with hand, foot and mouth disease (HFMD). During the outbreak, a total of 440 children were hospitalized in Hong Kong[1]. Among these, 165 children were admitted to the Paediatric Infectious Disease Unit (PIDU) of Princess Margaret Hospital (PMH)[2]. The following is a brief review of HFMD that we encountered in 1999.

From the discharge statistics of the PIDU of PMH, an increase in the number of admissions for HFMD was observed since May 1999 (Table 1). A total of 76 children (43 boys and 33 girls) were hospitalized for HFMD in 1999. Their age ranged from 2 months to 12 years (mean 3.1 years). 64 (84.2%) children were less than or equal to 5 years. All presented with typical clinical features of HFMD, including oral ulcers, vesiculopapular rash of the palms and soles, and some of them had similar skin rash involving the buttocks, knees and elbows.

Most of the children were hospitalized as a result of high fever or poor oral intake. 63 (82.9%) children were febrile, with admission temperatures ranging from 38°C to 40.5°C. 22 (28.9%) children required the administration of intravenous fluids for rehydration or supplementation. The duration of hospitalization ranged from 1 to 7 days (mean 3.2 days). Unlike the experience in 1998, none of the children developed neurological complication.

Specimens collected for identification of viral etiology included nasopharyngeal aspirates, throat swabs, rectal swabs and stool. Among the 76 children, viral etiologies were identified in 39 (51.3%) of them. Coxsackievirus A16, EV 71, Herpes simplex type 1, Adenovirus type 3, Adenovirus type 5 and Echovirus type 9 were isolated in 27 (69.2%), 7 (17.9%), 2 (5.1%), 1 (2.6%), 1 (2.6%) and 1 (2.6%) children, respectively. In 1998, among the identifiable viral etiologies, Coxsackievirus A (mostly A16), EV 71, Adenovirus and untyped enteroviruses accounted for 60.4%, 32.1%, 2.8% and 4.7%, respectively.[2]

From 1994 to 1999, the annual admission figures for HFMD at the PIDU, PMH peaked in 1998, during which time a total of 165 children were hospitalized and 2 developed neurological complications (Table 2). Public awareness of an outbreak of HFMD was heightened in 1998 through coverage in the mass media. Staff of our department has also

taken an active role in public education through media interviews and distribution of information pamphlets to parents of hospitalized children.

There was a significant decrease in the number of admissions for HFMD to the PIDU of PMH in 1999, with only 76 children hospitalized and none developed neurological complications. However, the total number of children with HFMD hospitalized for the whole of Hong Kong was 467, which was similar to that in 1998.[1] In May, 1999, a 2-year-old boy died of probable meningoencephalitis as a result of EV71 infection[3]. The child's 3-year-old sister and 6 other children in the same childcare centre in Yuen Long suffered from uncomplicated HFMD and made full recovery.

Compatible with the expected increase in incidence of HFMD during the summer months, the majority of admissions occurred within the months of May to August. Similar to 1998, the leading viral etiology for HFMD in hospitalized children in 1999 was Coxsackievirus A16, which is the other commonest cause for epidemic HFMD apart from EV 71.

The number of children susceptible to EV 71 infection was expected to be lower subsequent to the outbreak in 1998. Nevertheless, the virus has not disappeared from the local population altogether. It is probably only a matter of time that another outbreak of EV 71 occurs in Hong Kong again.

Month	**No. of admission**
Jan	0
Feb	0
Mar	1
Apr	0
May	13
Jun	15
Jul	22
Aug	11
Sep	5
Oct	5
Nov	2
Dec	2
Total	**76**

Table 1. Monthly admission figures for HFMD in PIDU, PMH, 1999

Year	**No.**	**No. with complication**
1994	7	0
1995	6	0
1996	7	0
1997	14	1 (aseptic meningitis)
1998	165	2 (1 EV71 aseptic meningitis) (1 EV71 meningoencephalitis)
1999	76	0

Table 2. Annual admission figures for HFMD in PIDU, PMH, 1994-1999

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The rise and fall of a rotavirus vaccine

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Rotaviruses are in the family *Reoviridae*, each member of which possesses a double layer of icosahedral shell and contains a core of double-stranded RNA. VP6, the major inner-core structural viral protein (VP) is responsible for the group specificity. Rotaviruses are divided into groups A through E. Human rotaviruses belong to group A, B or C. Most of the infections in Hong Kong are caused by group A rotavirus although group B strains were associated with several large outbreaks of gastroenteritis in China that affected adults as well as newborns in the nursery. VP7, the major outer capsid viral protein is responsible for the G (glycoprotein) serotype specificity of group A viruses. VP4, another capsid viral protein, is responsible for the P (protease-sensitive protein) serotype specificity. There are 10 G and 8 P serotypes of human rotaviruses known to man, resulting in 80 possible different strains. However, only 4 common strains P[8]G1, P[8]G3, P[8]G4 and P[4]G2 predominate globally although unusual strains can be common in developing countries. Serotype G1 is the most prevalent serotype infecting humans worldwide, although serotypes 2,3, and 4 may predominate in some countries during some seasons.[1-3]

Rotavirus infection has a short incubation of 1 to 2 days. Children and infants infected with rotavirus typically present with emesis initially, followed by profuse watery diarrhea. Rotavirus causes diarrhea in children resulting in dehydration and hospitalization. Worldwide, rotavirus is estimated to cause more than 125 million cases of diarrhea annually in children younger than 5 years of age, resulting in approximately 600,000 deaths. Diseases tend to be most severe in children between 3 and 24 months of age while infants younger than 3 months of age are relatively protected. The peak incidence of rotavirus infection in temperate countries occurs in winter while that in tropical and developing countries is less seasonal. The disease usually lasts 4 to 5 days.

RotaShield (Wyeth-Lederle), known as tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) in clinical trials, is a live-attenuated orally administered product derived from four group A rotaviruses. It was licensed by the United States Food and Drug Administration (FDA) on August 31, 1998. Three of the rotaviruses are single gene reassortants of the VP7 gene of human origin (types G1, G2, and G4). The fourth strain is rhesus rotavirus (type G3), which is antigenically similar to human G3. The Advisory Committee on Immunization Practices (ACIP), and the American Academy of Pediatrics and the American Academy of Family Physicians all recommended routine use of this vaccine in healthy infants.[4,5] Studies of rotavirus vaccine demonstrate that more than 88% of children respond to three doses of the vaccine. Studies with rotavirus vaccine in over 3000 children in the United States, Finland, and Venezuela demonstrated efficacy rates of 48% to 68% in preventing diarrhea caused by rotavirus, 38% to 91% in preventing moderate disease, and 70% to 100% in preventing severe disease. In Venezuela, rotavirus vaccine prevented dehydration and hospitalization in 75% and 70% of recipients, respectively. In Finland, rates of prevention of dehydration and hospitalization were 97% and 100%, respectively. Because none of the clinical trial data extend beyond 2 years, duration of protection beyond this time is uncertain, but protection similar to that after natural infection is expected. The rotavirus vaccine was recommended to be administered orally to infants at 2, 4 and 6 months of age. The first dose may be given as late as 6 months of age. Due to the increased rates of fever with age, initiation of immunization after 6 months of age was not recommended. Even if a child had had a documented episode of wild-type rotavirus gastroenteritis, he/she was still recommended to receive all 3 doses of the vaccine.

Prior to licensing, the contraindications and precautions for administering this vaccine was rather standard. The major side effects found were an increase in temperature $\geq 38^0$C, decreased appetite, irritability and decreased activity. The rotavirus vaccine was not

recommended for children with acute vomiting or diarrhea. Children who are known or suspected to be immunosuppressed or immunodeficient should not receive this vaccine.

Between September 1, 1998 and July 7, 1999, fifteen cases of intussusception in infants who had received RRV-TV were reported to the Vaccine Adverse Event Reporting System (VAERS). VAERS is a passive surveillance system operated by the FDA and CDC. Vaccine manufacturers are required to report to VAERS any adverse event reported to them and health-care providers are encouraged to report any adverse event possibly attributable to the vaccine. Vaccine recipients and their families can also report adverse events to VAERS directly. Investigation into the cases found that of the 15 infants with intussusception, 13 (87%) developed intussusception following the first dose of RRV-TV, and 12 (80%) of the 15 developed symptoms within 1 week of receiving any dose of RRV-TV. Intussusception was confirmed radiographically in all 15 patients. Eight infants required surgical reduction, and one required partial resection of distal ileum and proximal colon. Histopathologic examination of the distal ileum indicated lymphoid hyperplasia and ischaemic necrosis. In the pre-licensure studies, 5 cases of intussusception occurred among 10,054 RRV-TV recipients and 1 case occurred among 4,633 controls. The difference was not statistically significant. Since licensure, the manufacturer had distributed 1.8 million doses of RRV-TV as of June 1, 1999 and estimated that 1.5 million doses had been administered. When these cases of intussusception were reported and analysis was being done, CDC recommended postponing administration of RRV-TV to children. By October 1999, 102 cases of intussusception were reported. Analysis showed that there was a strong and significant causal relationship between RRV-TV and intestinal obstruction and the risk of intussusception was increased in the first two weeks after vaccination. At the end of October, 1999 the ACIP withdrew its recommendation for rotavirus administration and Wyeth Lederle voluntarily withdrew the vaccine from the market and recalled all distributed doses.

The withdrawal of this rotavirus vaccine which had been shown to be efficacious in both developed and developing countries was a great disappointment. However this incident shows that rare but serious adverse events may not be detectable in pre-licensing studies and underscores the importance of continuous post-licensure monitoring and reporting. While an increased risk of a potentially life-threatening intussusception was deemed an unacceptable price to pay in the United States where intussusception causes mainly morbidity, this may not necessarily be the case for developing countries. In such countries, whether the protection from the 600,000 annual deaths due to rotavirus each year outweighs a risk of 1 case of intussusception for every 14,705 doses of vaccine given may not be such an easy question. As for the quest of a protective rotavirus vaccine, all is not lost: a new type of rotavirus vaccine is under investigation. This vaccine, designated 89-12, is a live, attenuated human strain of rotavirus vaccine and two doses of which were found to have equivalent protection as three doses of the tetravalent reassortant vaccine.[6]

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A patient with unusual chest infection

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Case Report

A 67-year-old male chronic smoker had right upper lobectomy done four decades ago for pulmonary tuberculosis. He first presented to medical department for Pseudomonas (P) aeruginosa chest infection in March 1998. One month later he was re-admitted for increased sputum production and dyspnoea. One of his sputum samples revealed a few number of acid fast bacilli (AFB). Chest x-ray showed extensive fibrocalcific changes and underlying bronchiectasis. However there was no significant radiological difference when compared with films taken since 1993.

Standard anti-tuberculosis (TB) drugs ($HRZM_7$) were started, and he was transferred to chest hospital for further management in June 1998. Subsequently, sputum culture sent in May 1998 grew Mycobacterium (M) chelonae only and its clinical significance was doubtful. All anti-TB drugs were stopped in July 1998.

He was re-admitted for fresh haemoptysis in September 1998. There was no new radiological abnormality. Fibreoptic bronchoscopy did not show any endobronchial lesion. Bronchial aspirate for AFB smear and malignant cell was negative, but PCR for M. tuberculosis was positive. Two subsequent sputum samples also showed a few number of AFB. Thus anti-TB drugs ($HRZM_7$) were restarted and he was discharged in late October 1998.

He was admitted again for recurrent haemoptysis and marked constitutional symptoms in early November 1998. Pure growth of P. aeruginosa was isolated from his sputum. He was treated with several courses of anti-pseudomonas antibiotics including piperacillin-tazobactam, ceftazidime, ciprofloxacin, aminoglycoside. He continued to deteriorate despite four weeks of parenteral antibiotics and two months of anti-TB drugs treatment. His sputum for AFB smear was persistently positive. Four sputum samples and two bronchial aspirates all showed positive growth of M. chelonae. At that point, he was thought to suffer from unusual M. chelonae chest infection. In addition to anti-TB drugs, he was treated with parenteral amikacin and oral clarithromycin (according to culture sensitivity). After four weeks of special anti-M. chelonae treatment, his constitutional and respiratory symptoms improved markedly. His subsequent sputum smears became AFB negative. He received further 5 months of oral clarithromycin treatment and remained well.

Discussion

Despite supervised anti-TB treatment and various potent anti-pseudomonas antibiotics, the patient's condition continued to deteriorate. On the other hand, M. chelonae was isolated repeatedly from his bronchial secretion. Although pathology of M. chelonae chest infection could be diagnostic, transbronchial biopsy has not been attempted because of poor patient condition. Amikacin and oral clarithromycin were given according to the sputum culture sensitivity. Patient responded dramatically to the therapeutic trial.

Rapidly growing mycobacteria have previously been classified in group IV in the Runyon classification. Only Mycobacterium fortuitum and Mycobacterium chelonae (formerly M. chelonei) referred to as the M. fortuitum complex, are human pathogens. There are two recognized subspecies (ss) of M. chelonae: M. chelonae ss. chelonae and M. chelonae ss. abscessus. M. fortuitum contains three biovariants. The rapidly growing mycobacteria are ubiquitous in the environment and may be found in soil, water, and dust. These provide the usual source of human infection by skin and mucosal inoculation or inhalation into the tracheobronchial tree. There is no evidence that disease can be spread by expectorated airborne droplets, making respiratory isolation of patients with these organisms unnecessary.

In the past three decades, skin and soft tissue infections caused by these organisms have been documented. Most of these infections are nosocomial (postsurgical) or are secondary to accidental environmental wound contamination. Disseminated disease, particularly with M. chelonae, has also been documented. In human, colonization with M. chelonae is often transient, and many isolates from sputum are not indicative of infection. Bronchoscopic contamination with these organisms and isolates due to damaged bronchoscope had been recognized. The ubiquitous nature of these organisms means that caution should be

exercised with a diagnosis being made on the basis of cultures, which may either represent contamination of specimens or transient colonization. M. chelonae ss. abscessus is responsible for more than 80% of the lung disease, whereas M. fortuitum is almost always associated with soft tissue infection. The reason for this difference in pulmonary virulence is not clear. Pulmonary disease secondary to rapidly growing mycobacteria has been associated with esophageal motility disorders, malignancy, ankylosing spondylitis, rheumatoid arthritis, cystic fibrosis, sarcoidosis, previous granulomatous disease, chronic obstructive lung disease, and lipoid pneumonia. Colonization by rapidly growing mycobacteria may be more prevalent in these patients, making the determination of whether invasive disease is present much more difficult.

Patients with rapidly growing mycobacterial lung disease are usually in their mid-60s with disease rarely seen in patients less than 50 years of age. However, an underlying disease is frequently present in patients under 50 years of age. Women are as commonly affected as men. Unlike tuberculosis, there is no predilection for particular socioeconomic groups. Costicosteroid and other immunosuppressive drugs do not predispose to or appear to exacerbate lung infection with rapidly growing mycobacteria.

Diagnosis

Patient may present with insidious onset of cough, purulent sputum, dyspnoea, fever, haemoptysis, weight loss, easy fatigue, or history of recent recurrent episodes of acute bronchiectasis. Radiographic appearance may include solitary pulmonary nodules, apical cavity disease, nonspecific unilateral or bilateral infiltrates. There is no specific predilection of this organism for the apical portions of the lungs or areas of the lung damaged by fibrosis or bronchiectasis. Calcification of pulmonary lesion, pleural effusion, hilar adenopathy and bronchopleural fistula are rare. CT scan of the chest is particularly helpful when surgical intervention is considered for seemingly localized disease or for assessing the effect of chemotherapy since radiological evidence of resolution of the infection can be demonstrated sooner and more clearly. Mycobacterial cultures are usually found to be positive for the rapidly growing mycobacteria after the radiographic abnormalities have been discovered.

Histologically, in pulmonary or cutaneous disease due to the M. fortuitum complex, the acute inflammatory response generally persists in association with epithelial granulomas and giant cells regardless of the age of the lesion. AFB, when present, are seen in the centre of the microabscesses with the rapidly growing mycobacteria, rather than in the area of caseating necrosis, where they are seen with the tubercle bacillus. Thus, the presence in the lung of a dimorphic inflammatory response (i.e., both acute and granulomatous inflammation) in a lesion caused by an acid-fast organism is virtually diagnostic of infection due to the M. fortuitum complex.

Natural History

Natural history of M. fortuitum and M. chelonae lung disease is perhaps the least well understood. In general, it is the least aggressive of the mycobacterial lung diseases. Disease tend to remit spontaneously in some cases (even in a patient with cancer), to progress slowly over months to years, or to show no progression at all. Most patients who have chest radiographic abnormalities at the time of presentation have little or no change over months to years. They may have fleeting, soft infiltrates that seem to have little or no relationship to clinical symptoms. In general, if radiographic progression occurs, it does so very slowly.

Some patients, however, may show gradual progression of the disease and deaths directly due to the lung disease have been reported. Clinically, patients will have exacerbations of their disease that usually last four to six weeks. These symptoms then clear and are followed by months in which the patient feels better, at times almost normal. There is no correlation between symptoms and radiographic findings, and patients generally have acid-fast bacilli in sputum during both exacerbations and periods of clinical remissions. In fact, the episodic nature of the disease, which mimics exacerbations of bronchitis, is typical for most patients and is due to the mycobacterial disease alone.

Treatment

M. fortuitum and M. chelonae are universally resistant in vitro to all first line anti-TB drugs. No single agent is active against all isolates, although amikacin is active against most subspecies and biovariants. Whether more than one drug is necessary to prevent the emergence of drug resistance is unknown but seems reasonable when a large burden of organisms is anticipated. Because susceptibility varies by species and among subspecies and biovariants, susceptibility must be determined.

The most optimal treatment of rapidly growing mycobacterial lung disease has not been established. Combination therapy with amikacin plus cefoxitin or imipenem as well as monotherapy with macrolide had been proposed for M. chelonae chest infection (1). Resection could also be considered in those good surgical candidates with unilateral disease (2). Latest American Thoracic Society (ATS) Guideline also recommends two to four weeks of amikacin plus cefoxitin with or without resection (3).

For M. fortuitum chest infection, ATS recommends six to twelve months of therapy with two oral agents to which the M. fortuitum isolate is susceptible (3). However, some authorities recommend initial two to four weeks of treatment with amikacin and cefoxitin. If clinical improvement is noted within these periods, oral therapy with two or more drugs for another three months will be adequate (4).

References

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