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Editorial Board

Hepatitis B and C co-infection

S. T. Lai, Department of Medicine and Geriatrics, Princess Margaret Hospital

Introduction

Hepatitis B and C viruses are the most common causes of chronic liver disease in the world. Co-infection with both viruses is not infrequent because of the similar routes of infection. The rate of dual infection in a randomly selected healthy population in one study was 0.68% [1]. In HBV infection, the rate of HCV co-infection ranges from 10-30% [2]. One study found that the rates increased with age and became more common in subjects aged > 50 [3]. An underestimation of the incidence is likely owing to the lack of large-scale studies and the phenomenon of serologically silent occult HBV infection. Dual infection with HBV and HCV is associated with more advanced liver disease and an increased risk of hepatocellular carcinoma (HCC) [2]. Treatment of co-infected patients is thus a priority.

Viral interactions

HBV and HCV can interact in various ways. Chronic hepatitis B (CHB) patients co-infected with HCV have decreased HBV DNA polymerase and lower HBV DNA levels, demonstrating HCV can suppress HBV [4]. HCV superinfection in patients with CHB can lead to HBeAg and HBsAg seroconversion to their antibodies [5]. HBV, on the other hand, can less commonly suppress HCV replication. In co-infected patients, decreased HCV RNA levels may be found in those with active HBV DNA replication [6]. HBV/HCV dual infection can have a spontaneous HCV RNA clearance rate of 71% compared with 14% with HCV infection alone [7].

Because of the propensity of HBV and HCV co-infection to cause severe liver disease, their combined effect has been thought to be important in the pathogenesis of HCC. PCR was used to investigate the presence of HBV and HCV in the liver tissue from 38 patients with HCC in Taiwan. Co-infection with HBV and HCV was seen in nine patients (23%). Most had HBV alone (71%) and a few had HCV only. In a hyperendemic area, HBV is closely associated with the development of HCC but that infection with HCV may play a secondary role [8].

Clinical scenarios

In defining the features of HBV/HCV co-infection, four clinical scenarios have been established. They are (1) acute dual viral hepatitis, (2) superinfection of either virus in patients chronically infected with the other virus, (3) chronic dual viral hepatitis, (4) occult HBV infection in chronic hepatitis C:

1. The interaction in acute hepatitis B and C co-infection is similar to their interaction in chronic co-infection. Needle stick injury is the most common cause of such infection. Compared to acute hepatitis B infection alone, HBV/HCV co-infection causes less elevation of ALT levels, delayed appearance of HBsAg and a shorter duration of HBsAg antigenaemia, suggesting HCV suppression of HBV activity [9].

2. Superinfection by HCV in HBV infection can result in suppression of HBV replication, termination of HBsAg carriage and HBeAg seroconversion. It can also result in more severe liver disease and fulminant hepatitis. The mortality rate of such a flare can be as high as 10%. In the contrary, superinfection by HBV in chronic HCV infection is less common. There was one report of 2 patients with one showing fulminant hepatitis and the other showing suppressive role of HBV

on HCV infection. This category of patients may therefore have an increased risk of fulminant hepatitis and those who recover are at risk of chronic co-infection [10].

3. Patients with dually active HBV and HCV infection, as demonstrated by detectable serum HBV DNA and HCV RNA, are at the highest risk of progression to cirrhosis and decompensated liver disease. This situation is, however, very uncommon. Active HCV infection in an inactive HBsAg carrier is the most common finding. Less commonly, active HBV infection in patients with inactive or prior HCV infection occurs (HBV DNA +/ HBeAg +/ HCVRNA -/ anti-HCV+).

4. Occult HBV infection in chronic hepatitis C can present with low circulating levels of HBV DNA and lack of antigens and their corresponding antibodies (HBsAg, HBeAg, anti-HBs antibody and anti-HBe antibody). The only positive serological finding may just be IgG anti-HBc antibody. The patients have worse treatment outcomes than those with HCV mono-infection. They are likely to have more severe liver disease. Some may have greater histological activity and higher ALT levels [11].

Treatment

No standard care has been established for HBV/HCV co-infection. Generally, the same treatment inclusion and exclusion criteria should be applied for both co-infected and mono-infected patients. Treatment is recommended for active chronic hepatitis and cirrhosis prior to decompensation, basing on serological and virological variables.

Interferon alfa (IFN alfa) has been the most extensively studied antiviral for HBV/HCV co-infection. In a report from Taiwan, among 15 co-infected patients, only 1 (6.7%) responded to IFN with sero-clearance of HBV DNA and HBeAg. One patient had icteric hepatitis with rise in serum HCV RNA when HBV DNA was cleared. In this study, conventional IFN is of limited value in dual infection and has a potential risk of severe hepatitis if the clearance of HBV removes its suppressive effect on HCV. The largest prospective trial of IFN alfa involved 30 HBV and HCV co-infected patients (HBsAg + and HCV RNA +). Patients were randomised to receive 6 or 9 million units of IFN alfa 3 times weekly for 6 months. The higher dose of IFN alfa was more effective in clearing the HCV RNA and HBV DNA than the lower dose (31.2% and 100% vs 0% and 0% respectively, p=0.045). Overall, IFN alfa monotherapy induces sustained virological response (SVR) in HCV infection in 0% to 44% of patients, HBV DNA loss in 3% to 29%, and HBeAg loss in 7% to 100%, depending on the dosage and duration of treatment and patient variables [12].

Combination therapy had been used for co-infected patients. The drugs employed were IFN and ribavirin. SVR rates of HCV infection were 43%-69% and HBV DNA clearance rates were 11%-35%. Successful treatment of HCV was correlated with reactivation or flaring of HBV infection in up to 50% of patients [13]. Another combination is IFN plus lamivudine. In one study, 8 dually infected patients received IFN 5 MU TIW and lamivudine 100 mg per day for 1 year and lamivudine alone for 6 additional months. Post-treatment ALT normalised in 4 (50%), 3 of 8 (37.5%) had HBeAg clearance and 4 (50%) had SVR of HCV infection [14].

New agents like adefovir, entecavir, tenofovir, and emtricitabine may have utility in patients with HBV-dominant co-infection. Pegylated interferon will likely replace standard interferon for treatment of HBV/HCV co-infection.

Liver transplantation is appropriate for co-infected patients with decompensated liver disease or HCC who meet the standard criteria for transplantation. According to UNOS data, there were 14 patients transplanted for combined hepatitis B and C in the USA in 2004 and 434 have been transplanted for this indication since 1988. There are limited data on the post-transplant course of these patients.

HBV + HCV + HIV co-infection may occur together due to their shared route of transmission. This triple infection is most common among IV drug abusers. It results in a complex clinical scenario due to interaction of the HBV and HCV and impact of the HIV on the immune system. More severe liver disease may also be the outcome. The consensus is that infection of HIV must be controlled before treatment of viral hepatitis. Treatment algorithms are often extrapolated from results of trials of patients with either HBV/HIV or HCV/HIV co-infection. IFN plus ribavirin is associated with SVR rate of around 25% in HCV/HIV co-infected patients. Lamivudine has been used in HBV/HIV co-infected patients, but is associated with a high rate of resistance. The use of newer agents such as adefovir, entecavir, tenofovir, and emtricitabine is promising.

Assessment of the "dominant" virus is helpful in determining a treatment strategy. Exacerbations of liver disease after initiation of therapy have been described; likely due to loss of viral suppression from the successfully treated dominant virus. Patients must meet the inclusion criteria for standard treatment guidelines for either HBV or HCV mono-infection. IFN plus ribavirin treatment has been well studied and has proven efficacy in HCV dominant co-infection. In patients with HBV dominant disease, IFN with or without lamivudine is a reasonable option. Further studies of other HBV nucleos(t)ide analogues are needed. Future trials are also needed to assess the effectiveness of pegylated interferon as well as triple therapy with lamivudine, IFN, and ribavirin in co-infected patients. Referral to a transplant centre is indicated for patients with decompensated cirrhosis, fulminant hepatitis or HCC. Patients who have triple infection with HIV/HBV/HCV should have their care coordinated by an HIV specialist.

Conclusion

In conclusion, co-infection with HBV and HCV is not uncommon, especially within areas of high prevalence of hepatitis B. Treatment options mostly include IFN with or without lamivudine or ribavirin. Treatment decisions should be based upon the determination of the "dominant" hepatitis virus. The immune profile and recommendations are summarised in Table 1. Caution must be exercised in treating co-infected patients, as flares of the untreated virus may occur. No standard of care has been established for treatment of co-infected patients. Many studies are small and preliminary in nature. Larger randomised, controlled trials are needed to clarify the optimal treatment for such patients and the role of newer antiviral agents.

Summary of Immune Profile and Suggested Treatment

Immune profile	HBV DNA	HBsAg	HBeAg	HCV RNA	Anti-HCV	Possible treatments
Dually active	+	+/-	+/-	+	+	IFN alone IFN + ribavirin IFN + lamivudine
Active HCV in HBV carrier	-	+	-	+	+	IFN alone IFN + ribavirin
Active HBV in chronic HCV	+	+	+/-	+	+	IFN alone IFN + lamivudine
Silent HBV in chronic HCV	+	-	-	+	+	IFN alone IFN + lamivudine

Table 1: Summary of immune profile and corresponding treatment recommendations

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Myiasis and *Chrysomya bezziana* infestation in Hong Kong

Cindy W. S. Tse, Department of Pathology, Kwong Wah Hospital

Introduction

"Myiasis" is a term derived from the Greek word of "myia" which means fly. It means the infestation of live human and vertebrate animals with dipterous larvae which feed on the host's dead or living tissue, liquid body substances or ingested food. Maggots can infest any organ or tissue which is easily accessible or exposed for the female flies to lay eggs or larvae. There are numerous cases reported worldwide especially in the developing countries or in the tropical climates, but most of the cases are from debilitated or Paediatrics patients. It is believed that the fly can drop its eggs during its flight on the skin, wounds, or natural openings of an immobile person.

There are many types of flies which can cause the disease of myiasis and usually the types of flies depend on their geographical distribution. *Chrysomya bezziana* is the most common species found in Hong Kong causing the disease. It belongs to the metallic group of the Calliphorinae family and it is also called the "Old World screwworm".

Types of myiasis

Myiasis can be classified into accidental, facultative or obligatory: in accidental myiasis, the larvae have no requirement for living in mammalian tissue; in facultative myiasis, the larvae live in dead tissue but may move into adjacent living tissue; but in obligatory myiasis, the larvae only live in living tissue. The types of myiasis can also be defined by the site of infection or affected tissues, e.g. cutaneous and mucocutaneous tissues of the eye, nose and throat, gastrointestinal tract, genital tract, lung or urinary tract were also reported.

Chrysomya bezziana is one of the causative organisms of obligatory myiasis.

Chrysomya bezziana and clinical manifestations

Chrysomya bezziana is widely distributed throughout Asia, including China and neighbouring regions of Hong Kong like Guangdong, Guangxi, Yunnan and Taiwan. It is also found in tropical Africa, the Indian subcontinent and Papua New Guinea. *Chrysomya bezziana* larvae are usually found on wounds and ulcerated skin surfaces of human and animals such as cattle, buffaloes, sheep, horses, dogs, camels and elephants. The infestations can also occur in patients with normal skin. It is important to identify *Chrysomya bezziana* because it can cause tissue invasion and destruction in the absence of pre-existing necrotic tissue. Feeding activity of the larvae may cause serious tissue damage.

The adult female flies like to lay eggs on live mammals, 150 to more than 200 eggs are deposited each time. The eggs hatch in 24 hours and the resulting larvae burrow and feed on host's living tissue. It takes around 5-7 days for them to finish feeding and then they will pupate after crawling out from the live tissue. The eggs can develop into adults in around 12-14 days in ideal situation of warm climates. The adult flies usually live for 2-3 weeks.

The site of infestation is usually on superficial wounds, open sores or ulcers, scratches and mucous membranes in body orifices such as the mouth, ear and nose. There are 2 case series and 1 case report from Hong Kong on myiasis caused by *Chrysomya bezziana*. In the case series reported by Chan JC et al, eight patients

were nursing home residents with an average age of 81.8 years. Seven patients were bedridden with advanced dementia. Most of the patients had poor oral hygiene and four of them were on tube feeding. All patients with poor oral hygiene suffered from oral myiasis. Two patients had vaginal infestations and one had wound myiasis in his diabetic foot ulcer. Lui CW et al also reported that most of the victims are debilitating elderly institutionalised in nursing homes and not ambulatory. Their daily activities may depend on nursing staff or others to help which predisposed them to the infestation. The myiasis can also be found in mentally retarded patients or children who have lower awareness on their self-hygiene. Cases were also reported in the homeless children who also have problem of maintaining good hygiene.

Management

The most common presentation is notice of “worms” crawling out from the site of infestation by others or patients complaining of itchiness or discharge from infected orifices. The most immediate and direct method is removal of the maggots by forceps as far as possible and sending the maggot for identification. This can be followed by irrigation with warm saline solution. Radiological assessment on the extensiveness and surgical exploration is indicated to remove the damaged tissues and deep-seated larvae especially around vital organs like the head and neck regions. As for ocular myiasis reported by Lui CW et al, early diagnosis is important in preventing extensive tissue damage and morbidity. Medical staff who take care of aged or debilitated patients need to be aware of this condition to enable prompt diagnosis and relevant intervention. There may also be secondary bacterial infections associated with the myiasis. The most common bacteria include *Staphylococcus aureus* and *Streptococcus* species. Antibiotic coverage may be warranted if bacterial infection is suspected.

Infection control measures

Myiasis is not transmitted by human to human. Standard precaution and keeping good personal hygiene of the debilitated and susceptible patients is adequate to prevent transmission. Remove all larvae from the infected wounds or areas. Also important is to remove any pupae or adult flies if seen around in the patient’s area and keep the environment clean.

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A case of pneumonia with travel history — Coccidioidomycosis

W. S. Li, Integrated Medical Service, Ruttonjee & Tang Shiu Kin Hospitals

Case presentation

A 50-year-old gentleman who was an ex-smoker, enjoyed good past health, presented with 2 weeks history of non-productive cough, associated with flu-like symptoms, malaise, poor appetite and weight loss. Ten days ago, he returned from a 9-day trip in Southwestern United States. He had visited South California (Los Angeles, San Francisco), Nevada (Las Vegas) and Arizona (Hoover Dam and Grand Canyon).

Physical examination showed left lower zone crepitations and an enlarged non-tender right supraclavicular lymph node. Chest x-ray showed left lingular consolidation (Figure 1). Blood tests showed normal total white cell count with mildly elevated eosinophils, otherwise were unremarkable. He was empirically treated with oral antibiotic as community acquired pneumonia and worked up for suspected bronchogenic carcinoma.

Computerised tomography of thorax with contrast showed atelectasis of medial portion of left lower lobe with air bronchogram. There were also multiple enlarged mediastinal lymph nodes and lung nodules in bilateral lower lobes, bronchoscopy showed presence of mucosal infiltration of the left main bronchus and left lower lobe bronchus suggestive of bronchogenic carcinoma. Endobronchial biopsy and bronchoalveolar lavage did not show evidence of malignant cells. Excisional biopsy of the right supraclavicular lymph node was performed and showed presence of spherules diagnostic of coccidioides infection (Figure 2). Typical mycelial and arthroconidia of the fungus were seen in the fungal culture. His clinical and radiological condition improved without any treatment and was followed up in out-patient clinic for serial monitoring. Six months later, he complained of a right groin mass clinically compatible with skin abscess. Incision and drainage of the skin abscess was performed. The pus was cultured positive for coccidioides immitis. He was diagnosed to have initial self-limiting coccidioides pneumonia complicated with extrapulmonary non-meningeal manifestation. Oral fluconazole 400mg daily was given for six months. Follow up bronchoscopy and serial chest x-rays showed resolution of the lesion.

Discussion

Coccidioidomycosis is caused by coccidioides immitis, a dimorphic fungus that grows as mold in the soil. It is transmitted by inhaling the spores (arthroconidia). A prospective study of cases of coccidioidomycosis showed that more than 60% were asymptomatic and resolved spontaneously. In symptomatic patients, pulmonary illness ranges from a self-limited flu-like illness to pneumonia. Approximately 5% of primary infections are associated with erythema nodosum or erythema marginatum with associated non-infectious arthritis. Multiple thin-walled chronic cavities may develop, especially in diabetic patients, as a residual effect of pulmonary coccidioidomycosis. Dissemination usually becomes evident within a few weeks of the primary pneumonia. Limited dissemination may become clinically evident months later. Common sites of extrapulmonary disease are soft tissue abscesses, bone and joint infection, and meningitis.

Treatment options

The severity of coccidioides infection varies so widely that the optimal management strategies vary widely among individual patients and generates debates.

Specific antifungal therapy for the treatment of coccidioidomycosis include amphotericin B (0.5-1.5mg/kg per day or alternate day administered intravenously), lipid formulation of amphotericin B (2.0-5.0mg/kg or greater per day administered intravenously), ketoconazole (400mg daily orally), fluconazole (400-800mg orally or intravenously) and itraconazole (200mg twice or thrice daily orally). Amphotericin B is usually reserved for severe infection with rapidly progressing disease. Fluconazole has been shown to have a trend towards better efficacy when compared with itraconazole in treatment of skeletal form of disseminated infection.

Newer therapy options are being studied while adjunctive therapy with interferon gamma in critically ill patients has also been reported with favourable results.

MANAGEMENT OF VARIOUS CLINICAL FORMS

Uncomplicated acute coccidioidal pneumonia

Primary infection due to coccidioides species most frequently manifest as community acquired pneumonia one to three weeks after exposure. Patients who present with early infections usually resolves without specific antifungal treatment. Management should include serial follow up every 3 to 6 months for up to 2 years, either to document radiographic resolution or to identify evidence of pulmonary or extrapulmonary complications.

Treatment should be started for symptomatic patients to decrease intensity and duration of symptoms, especially in patients with concurrent immmunosuppression such as AIDS, organ transplant recipient, on high dose corticosteroid treatment, or recipients of tumour necrosis factor inhibitors. Consideration should also be paid to patients with diabetes or pre-existing cardiopulmonary disease in initiation of treatment.

Patients should be assessed for clinical indicators for severity of clinical disease: weight loss of >10%, intense night sweats persisting longer than 3 weeks, infiltrates involving more than one-half of one lung or portions of both lungs, prominent or persistent hilar adenopathy, anticoccidiodial complement fixing antibody concentration in excess of 1:16, inability to work, symptoms that persist for >2 months, or age >55 years.

Diffuse pneumonia

Diffuse pneumonia in immunocompetent patients usually present with multiple sites of infection and treatment is needed to lessen the fungal load. Azole therapy is preferred while amphotericin B is reserved for very ill patients. In immunocompromised patients, acute diffuse pneumonia present with bilateral reticulonodular infiltrates that progress to respiratory failure rapidly. Amphotericin B is the initial treatment of choice. When condition is stabilised, treatment with an azole should be continued until immune state has reconstituted, and some may need lifelong therapy.

Asymptomatic pulmonary nodule

Asymptomatic nodules or completely resected nodules do not require specific therapy and usually spontaneously resolve in the first two years after infection. Serial radiographic monitoring of size of nodule for two years is recommended. Re-evaluation with sputum culture and serum antibodies may help to determine the activity of infection and guide therapy. Therapy is needed when patient is

immunocompromised.

Pulmonary cavity
Asymptomatic cavities do not require specific antifungal therapy and often resolve within several years, continued monitoring is required. When symptoms such as pain, haemoptysis appear, or superinfection with other fungi or bacteria, azole antifungal treatment may improve symptoms but does not close the cavity, and symptoms may recur on cessation of treatment. Cavities that persist for more than two years with symptoms, adjacent to pleura, or increase in size may warrant surgical resection to avoid complications such as rupture into pleural space leading to pyopneumothorax.

Chronic progressive fibrocavitary pneumonia
As the progression of this disease entity is slow, azole is used as initial treatment, while amphotericin B is used when condition is deteriorating rapidly until stabilised and switch over to azole group. The treatment should be continued for at least one year. Surgical resection may be used for refractory localised lesions or cases with severe haemoptysis.

Disseminated infection (extrapulmonary)
For nonmeningeal extrapulmonary infection, oral azole antifungal treatment is the preferred initial treatment. Amphotericin B is recommended as alternative treatment if lesion is worsening rapidly or in critical locations. When infection is widespread or failed on single treatment, combination therapy may improve clinical response, but there is no evidence showing combination therapy is superior to single treatment. Surgical intervention may be considered in lesions with increasing size, presence of bony sequestrations, spine or critical organ involvement.

For meningitis, oral fluconazole 400mg per day is currently the preferred treatment of choice. Itraconazole 400 to 600mg per day has also been comparably effective. Intrathecal amphotericin B should be considered with or without concurrent azole therapy in patients non-responding to azole as initial treatment. High dose, intravenous, short term corticosteroids may be considered to prevent complications of cerebral vasculitis leading to cerebral ischaemia, infarction and haemorrhage. Shunt decompression is needed when hydrocephalus developed as complication.

Conclusion
Coccidioidomycosis is endemic in south-western part of the United States, Central and South America. It is not commonly seen in our region, but should be considered as a possible cause of radiological abnormality in immunocompetent patients returning from endemic areas or in immunocompromised patients with disseminated disease who had visited the endemic areas. Depending on the clinical entities of infection, different management strategies are employed.

Figure 1. Chest x-rays of the patient on presentation showing left hilar mass

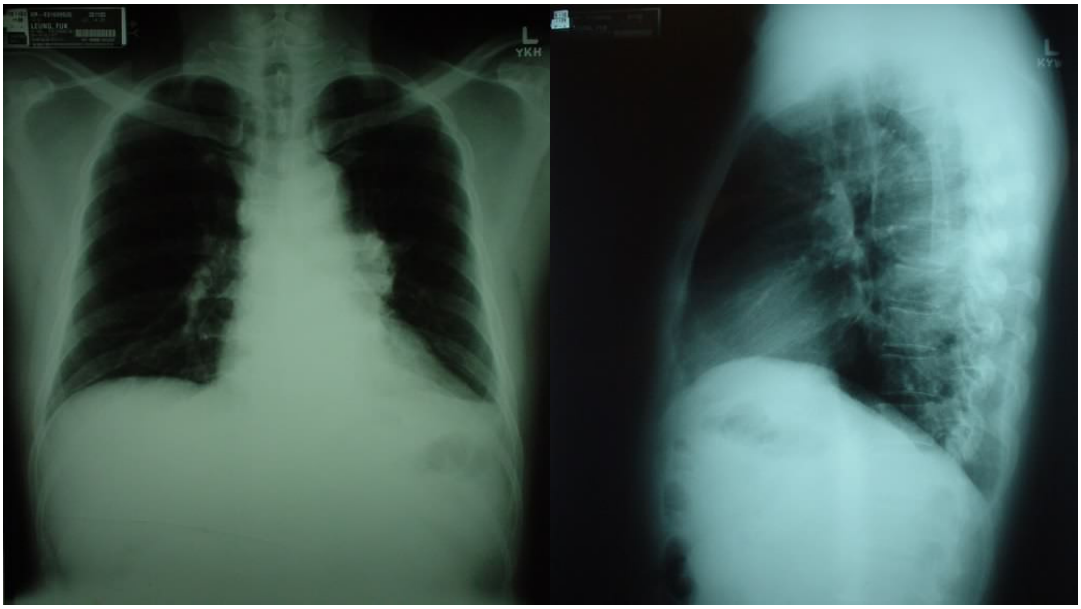
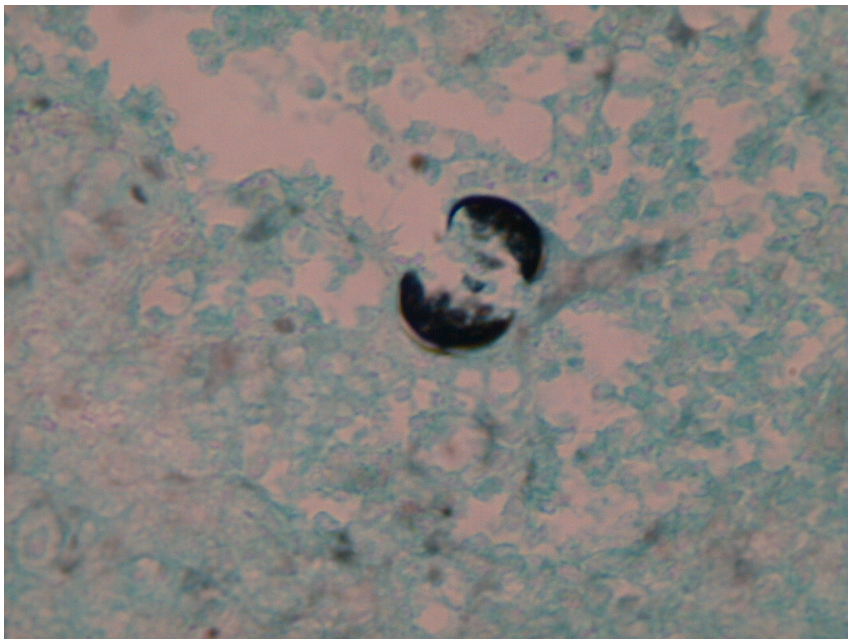


Figure 2. Excisional biopsy of the right supraclavicular lymph node with Grotton stain showing the presence of a spherule erupting and the released arthroconidia.



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Journal review

Alan K. L. Wu, Department of Pathology, Pamela Youde Nethersole Eastern Hospital

de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med. 2005; 353: 2667-72.

During the current influenza A (H5N1) pandemic among birds, less than 200 human cases have been reported worldwide. One potential approach to treating human infections with H5N1 is the use of oseltamivir, a neuraminidase inhibitor. However, the efficacy of such treatment has been called into question recently, as a group of investigators now report the finding of H5N1 resistance to oseltamivir in two Vietnamese patients with lethal infections.

Eight patients admitted to hospital with documented H5N1 infections were treated with oseltamivir, and four survived while four died. Throat specimens obtained from two patients with fatal outcome yielded H5N1 viruses with an H274Y substitution in the neuraminidase gene, a specific mutation known to confer high-level resistance to oseltamivir. In one of these two patients, viral drug resistance was thought to have developed during therapy. The clinical condition of the second patient was initially stable during the first 3 days on oseltamivir, only to be followed by rapid clinical deterioration. In contrast, no virus was detectable at the end of oseltamivir treatment in three of the patients who survived.

Points to note: This study showed that oseltamivir-resistant virus with the H274Y mutation can develop during therapy. Obviously, it raised more questions than could be answered at this stage. For instance, will higher drug doses be necessary for optimal viral suppression, and should the drug be used for longer periods? Could drug-resistant viruses be transmitted? A clear message should be sent to the general public: that stockpiling of oseltamivir by the public must be stopped, because improper use of this agent will likely increase drug-resistant influenza virus populations, and the result would be disastrous.

Vesikari T, Matson DO, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med. 2006; 354: 23-33.
Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med. 2006; 354: 11-22.

The global healthcare and economic burden of rotavirus gastroenteritis (RG) is truly enormous. Just consider these figures: RG results in 25 million clinic visits, 2 million hospitalisations, and 600,000 deaths in young children worldwide every year, mostly in developing countries. The first rotavirus vaccine, Rotashield, was soon withdrawn from the market after licensure in the United States in 1998 because of an association with intussusception. Two other rotavirus vaccines have since demonstrated safety, immunogenicity, and protection, and researchers have now examined the efficacy and safety of these vaccines in large-scale, company-sponsored trials.

Vesikari and colleagues studied Rotateq, a live pentavalent vaccine containing five reassorted human-bovine rotaviruses, covering a variety of human rotavirus

serotypes (G1, G2, G3, G4, and P[8]). Approximately 70,000 healthy 6 to 12-week-old children in 11 countries were randomised to receive 3 oral doses of Rotateq or placebo and followed for 42 days. Intussusception occurred within 42 days after any dose in 6 vaccinees and 5 placebo recipients, and within 1 year in 12 vaccinees and 15 placebo recipients. The vaccine was shown to reduce hospitalisations and emergency department visits for RG serotypes G1–G4 by 94.5% and hospitalisations for all gastroenteritis by over 50%. Efficacy against severe G1–G4 RG was as high as 98.0%. A modest protective effect against RG was still detectable in the second rotavirus season.

Ruiz-Palacios and colleagues studied a live attenuated human rotavirus vaccine with G1P[8] specificity (Rotarix) in 63,000 children in 11 Latin American countries and Finland. Participants were randomised to receive two oral doses of vaccine or placebo. Thirteen cases of intussusception (6 in the vaccine group, 7 in the placebo group) occurred within 31 days of either dose, while 12 additional cases (3 in the vaccine group, 9 in the placebo group, P=0.08) occurred thereafter. The vaccine group had significantly lower rates of hospitalisation, serious adverse events, and gastroenteritis-related morbidities. Use of the vaccine was associated with a 42% reduction in the rate of hospitalisation for diarrhoea due to any cause. Vaccine efficacy was over 80% against hospitalisation for severe RG, and protective efficacy was related to the infecting rotavirus serotype.

Points to note: Like Rotashield, these new vaccines effectively reduced the incidence of RG, especially for more severe forms of the disease. Importantly, they did not seem to increase the risk of intussusception, as demonstrated in these large clinical trials. Nevertheless, the prospect of widespread use of rotavirus vaccines, especially in developing countries where they could have the greatest effect, may be limited by economic and logistic considerations.

Hoelscher MA, Garg S, Bangari DS, et al. Development of adenoviral-vector-based pandemic influenza vaccine against antigenically distinct human H5N1 strains in mice. Lancet. 2006; 367: 475-81.

With the risk of emergence of pandemic due to avian influenza in the human population, development of an H5N1 avian influenza vaccine that is safe and effective is an urgent research priority. Investigators recently developed an adenoviral-vector–based vaccine (HAd-H5HA) with hemagglutinin from an H5N1 human isolate (Hong Kong, 1997) and tested it in a mice model.

The replication-defective recombinant human Ad-vector–based vaccine with the H5 gene was tested in a group of BALB mice. Other groups of animals received injections of saline alone, vaccine with the H5 gene deleted (HAd-E1E3), or a traditional subunit vaccine (with and without alum adjuvant). Four weeks after the second injection, the mice were challenged with a lethal dose of a related H5N1 virus. Other mice were inoculated intramuscularly or intranasally with HAd-H5HA or HAd-E1E3 and challenged with H5N1 isolates from 2003 or 2004.

HAd-H5HA induced cellular and humoral immunity to H5N1, and was successful in protecting challenged mice against viral replication, disease, and death. Although intramuscular and intranasal routes of delivery were both immunogenic, intramuscular route appeared to generate a more robust response after vaccination.

Points to note: H5N1 vaccines currently being tested in humans require embryonated eggs for production and appeared to be only modestly immunogenic. These drawbacks make it unlikely that large supplies could be produced rapidly, as might be necessary with a pandemic situation. Ad-vector–based vaccines can be grown in cell culture and do not require eggs for production. Phase I to phase III clinical trials are currently underway with other Ad-vector–based vaccines to further explore the usefulness of this approach.

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