

SARS: Just another viral acronym?

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Summary Recent observations and experimental evidence have purported that a virus causes SARS, but such viruses have been isolated in only less than half of SARS patients in some studies and virologist Vincent Plummer of Winnipeg's National Microbiology Laboratory found that indeed 1 in 5 perfectly healthy Canadians with a history of recent travel to Asia *had* the virus. Therefore SARS microbiologic origins remain unclear.

Outbreaks of multi-drug resistant (MDR) tuberculosis and the atypical mycobacteria simulate SARS on clinical, radiologic, epidemiologic, and diagnostic laboratory grounds and it is only logical then to include them in the differential to find a definitive cause and cure for SARS.

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In the middle of March, 2003 an unusual but deadly outbreak of atypical pneumonia in a Hong Kong hospital ward started incapacitating Chinese medical personnel. Within one week its case rate, through contact spread, spiraled and it began to appear not only in other countries in the region, but Europe, North America and Australia.

CDC began supporting the World Health Organization (WHO) in the investigation of a multi-country outbreak of the atypical pneumonia of unknown etiology (1), referred to as severe acute respiratory syndrome (SARS).

SARS appeared to be infectious. Fever, followed by rapidly progressive respiratory compromise were the signs and symptoms from which the syndrome derived its name. But its microbiologic origins remained unclear (2).

Virologists were certain that SARS, fast evolving into the first global health crisis of the 21st century, was a virus.

They posited that like AIDS, the world was being engaged by yet another deadly four-letter viral acronym. The Chinese first had isolated an avian influenza A (HSN) virus, however this 'bird flu', possibly from

poultry, was soon ruled out. Then human metapneumoviruses (hMPV) was noticed but could not be verified in other laboratories. Simultaneously Chinese scientists found a chlamydia-like organism taken from patients during what later came to be known as the Guangdong outbreak, where death came within hours. But again this could not be confirmed in most laboratories outside of China. Finally, on April 16, 2003, a novel coronavirus, never before seen in human or animals was proclaimed by WHO officials to cause SARS. Up to this point human strains of coronavirus were only associated with mild disease and never known to kill so precipitously. Also, a much larger problem was that in some studies (3) coronavirus was present only in about half of the SARS cases, while in others only 40%, and began to look more like just another passenger virus than anything else. Besides this, antivirals such as ribavirin and oseltamivir (Tamiflu) were not working on SARS culture plates, nor were they very successful clinically either.

Isolation of the corona virus was done by culturing whole tissue isolates of respiratory secretions, blood or stool on a live Vero cell line from the kidneys of green monkeys kept alive since 1962. Positive cell culture results show the presence of live virus which in the case of coronavirus were then used to infect monkeys at Erasmus University in Rotterdam, which came down with symptoms similar to SARS. Several problems in methodology and thought immediately surfaced. First, how did one know that this member of the coronavirus family, never seen before in humans, was actually a virus. There are many viral forms of bacteria, especially

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the mycobacteria, which simulate and look like viruses in every way and are also found in respiratory secretions, blood and stool (17). Secondly, even if it was indeed a virus, how could one testify to the purity of the monkey inoculate (bacteria also grow in Vero Cell cultures). Last, if corona virus was indeed the cause of SARS why was it not found in all SARS patients.

Coronaviruses are ubiquitous, causing illness in many animals, including pigs, cattle, dogs, cats and chickens and have been associated with gastroenteritis, upper respiratory infections and from time to time pneumonia, in humans. All of this however is neither the exclusive domain of the coronaviruses nor any other virus. Mycobacteria, such as *Mycobacterium avium*, and *Mycobacterium bovis* also inhabit these animals and *M. avium* has been associated with upper respiratory infections and sometimes pneumonia in humans.

Furthermore, mycobacteria such as tuberculosis and the atypical forms of tuberculosis are just the kind of pathogens that can lead to the abrupt death witnessed in Guangdong. In 1990, a new antibiotic-resistant tuberculosis outbreak took place in a large Miami municipal hospital. Soon similar outbreaks broke out in three New York city hospitals from which it spread to city prisons. Like the origin of SARS, the infection spread in nosocomial manner – from patient to patient and from patient to staff. As in Florida multi-drug-resistant strains made the New York TB cases almost impossible to treat and the majority of sufferers died, many within weeks (23).

It is only logical then to investigate whether mycobacteria such as these Non-Tuberculosis Mycobacteria (NTMB), *Mycobacteria tuberculosis* or multi-drug resistant tuberculosis, are the real pathogens underlying SARS. Certainly the droplet transmission that seems so important in the unusually rapid spread of SARS speaks for an airborne droplet nuclei vector of less than 10 μm in diameter (4), a must for the successful transmission of *M. tuberculosis*. But that is not all.

COMMON GROUND

In Poutanen's study of Canadian SARS, her subjects were either from an Asian family that lent itself to 'concern about possible tuberculosis in the family' (3), had had exposure to that family, were Asian, or reported recent travel to Southeast Asia, itself endemic for tuberculosis.

Wong's comprehensive study on thin-section CT of 73 patients exposed to or coming down with SARS (5) found that the lower lobes were preferentially affected, especially in the early stages. Atypical radiologic manifestations of TB, encountered in as many as one third of cases include such lower infiltrates. And lower lobe predominance is seen even more commonly in nontuberculous mycobacterial infection. In advanced SARS cases, perihi-

lar enlargement, was noted, a hallmark of TB. In addition, the majority of the lesions contained an area of ground-glass opacification with or without consolidation. Ground-glass findings are a predominant finding in high resolution CT (HRCT) of miliary tuberculosis and of 25 TB patients, Hong observed 23 with areas of ground-glass opacities, a sign of active infection (6).

Wong's other SARS CT findings were intralobar septal thickening, a 'crazy-paving' pattern (a network of smooth linear patterns superimposed on an area of ground-glass opacity on thin-section CT) and bronchiectasis. All of these findings are possible with tuberculosis and the related mycobacteria. By Laissey's criteria, the bulk of Wong's findings seem like HRCT findings of a nontuberculous mycobacterial (NTMB) pulmonary infection (7), although there is considerable overlap between TB and the other mycobacteria in Laissey's study. Yet Wong's differential list of possible SARS causes does not for some reason mention mycobacterial disease, choosing instead: 'other causes of atypical pneumonia.'

Mangura et al. (8) reiterates that tuberculosis can easily simulate 'atypical pneumonia', and Steponaviciene (9) reminds that clinical symptoms of TB pneumonia are most similar to the atypical pneumonia caused by *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.

Even on a clinical and laboratory basis it seems that SARS and miliary tuberculosis match. Fever, leukopenia, thrombocytopenia, lymphopenia and hypertransaminasemia are all present (10). Mert even raises the point that either miliary infiltrates on a chest X-ray or fever of unknown origin (FUO) should raise the possibility of miliary TB and that therapy should be administered urgently to prevent an otherwise fatal outcome. In many parts of the world tuberculosis is still not only the most common infectious disease but the commonest cause of fever of unknown origin, recurrent or otherwise.

Although high fever, nonproductive cough, low blood oxygen saturation, and varying degrees of respiratory distress, all found in SARS, are nothing new to the clinical picture of tuberculosis (11), the number of TB cases in which people in the Orient die of adult respiratory distress syndrome (ARDS) is definitely on the rise (12), the same ARDS that often provokes the 'crazy-paving' appearance at thin-section CT (13). Chen cautions that in considering the relatively high incidence of pulmonary tuberculosis in China, the percentage of miliary tuberculosis as a potential cause of ARDS 'might not be very low' (14). Roger, among others favors suspecting tuberculosis in all cases of acute respiratory failure of unknown origin (15). One thing is certain, ARDS caused by miliary TB is associated with just as high a fatality rate as ARDS caused by SARS (16).

Perhaps one of the most puzzling features to virologists regarding SARS is that compared with adults and

teenagers, it seems to have a less aggressive clinical course in younger children (22); puzzling until one reads bacteriologist Dubos's observation that tuberculosis is rarely severe between the ages of 5 and 12 (23).

DIAGNOSTIC DIFFICULTIES

Roger urged treatment for TB in all cases of ARDS of unknown origin even in cases of negative chest X-ray and a negative though exhaustive microbiology search. Rogers words are well taken. Tuberculosis and the mycobacteria are at best quite difficult to detect, especially when in their viral-like, dormant, L-form configurations (17).

Bacterial L-forms, the connecting link between viruses and bacteria, were first described by Klieneberger at England's Lister Institute for which they were named. L-forms are 'cell-wall deficient' because they either have a disruption or lack of a rigid bacterial cell wall. This lack of rigidity allows them the plasticity to assume many forms (pleomorphic), some of which are viral-like but all different from their classical parent and poorly confirmed by ordinary staining (18). Of all the bacteria, L-forms predominate and are crucial to the survival of the mycobacteria, whose cell-wall deficient (CWD) forms escape destruction by the body's immune system. At the same time many of these mycobacterial L-forms, are variably acid-fast, meaning that depending upon what stage they are in they only intermittently pick up acid-fast stain, classically used to detect TB.

TREATMENT OPTIONS

MDR resistant tuberculosis has been on the rise for some time. Chilling examples include recent outbreaks of MDR-TB and the appearance of macrolide-resistant *M. avium* (19).

Many of the radiologic features of SARS favors a possible non-tuberculous mycobacterial (NTMB) cause. But one of the hallmark characteristics of the NTMB *M. avium* is its resistance to most of the anti-tuberculosis drugs and the documentation that respiratory distress can be precipitated by classic TB medicine is well taken (20).

By the same token steroids in tuberculous infection are reportedly ineffective or risky and should only be administered in an attempt to thwart off the most dire respiratory emergency and then only in conjunction with appropriate antibiotics.

No one knows at this juncture whether SARS is from typical or atypical mycobacteria or a combination of both and once initial cultures are drawn a more prudent approach might be to start these patients off with a course of NTMB therapy including Amikacin (renal function permitting) and a macrolide such as Azithromycin (21). After 7–10 days of this combination low dose

antimycobacterials can be introduced along with continued Azithromycin.

Other pathogens which can cause respiratory distress and fever must be ruled out, including Malaria (by serology and thick and thin smears) where appropriate.

SUMMARY

By 1992 multi-drug-resistant (MDR) tuberculosis had appeared in seventeen US states, with mini-epidemics in Florida, Michigan, New York, California Texas, Massachusetts and Pennsylvania and was reported by the international media as out of control.

MDR TB has been the focus of attention for some time and seems extremely important in a disease that killed one billion people between 1850 and 1950 alone (24), not to mention the 2.7 million it now kills each year. That the strain of this disease with the label SARS should join this slaughter is strongly supported by similarities it shares with the mycobacteria beyond coincidence.

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