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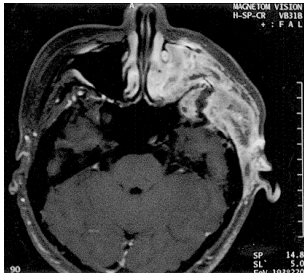
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Cover Picture:

Pre-operative CT scan showing an osteoblastic tumour rising from the sphenoid bone extending to the temporal, fronto-orbital and zygomatic bones and involving the temporalis muscle with sparing of the periorbital and orbital contents and dura covering the frontal and temporal lobes.  
(Refer to page 586-589)

## Rickettsioses: The New and Old Diseases

SY Wong, M S Lam

Rickettsioses represent some of the oldest and newest known infections in man. From as far back as the 5<sup>th</sup> century B.C., a rickettsiosis, epidemic typhus, was thought to be the cause of the Athens plague<sup>(1)</sup>. Since then, mankind has been repeatedly subjected to infections from Rickettsia species. Rickettsiae are fastidious, mostly obligate bacterial organisms that are intracellular parasites. They are widely distributed throughout the world and many of the newly identified strains are associated with clinical types of spotted fever that have been previously described from Asia and Africa. The pathogenesis of infection involves a vasculitis caused by the proliferation of the organisms in the endothelial linings of the small arteries, veins and capillaries. Traditionally, the rickettsioses have been classified into spotted fevers and typhus syndromes but we now know that there is a wide spectrum of clinical disease including encephalitis, endocarditis, pneumonitis, hepatitis, meningitis and septic shock<sup>(1,2)</sup>. As the rickettsiae are intracellular parasites requiring host cells in which to replicate, the traditional isolation and identification methods in bacteriology are not useful. The recent discovery of new strains of Rickettsiae underscores the marked progress in advances made in the areas of diagnostic capabilities and the use of cell culture and molecular techniques<sup>(1)</sup>.

In this issue, we are once again reminded that typhus fever still occurs in significant numbers in Singapore<sup>(3,4)</sup>. Increasing travel<sup>(5)</sup>, poor housing conditions in selected patient populations<sup>(3,4,6)</sup> and the development of more sensitive serological tests will see an increase in the number of cases diagnosed. The disease remains largely under-recognised and a lot of wasted resources may be directed towards expensive PUO work-up if this condition is not considered<sup>(6)</sup>. Locally, the disease epidemiology is strongly associated with poor and unhygienic living conditions, especially amongst the foreign immigrant workers<sup>(3,4,6)</sup>. More needs to be done to ensure these workers are provided improved living quarters. However, the Singapore residents are not spared. Ong et al<sup>(4)</sup>, reported that local residents were also infected and suggested that there was cross transmission and a spillover effect from the immigrant worker population. Similar factors and spillover from the rural areas may also explain the increase of typhus fever seen in Kuala Lumpur<sup>(7)</sup>.

For the clinicians familiar with this disease, making a diagnosis of probable typhus fever is often not difficult. However to the uninitiated, making an early definitive diagnosis remains deceptively difficult. Historically, the Weil-Felix test is the prototype of serological tests used in diagnosis of rickettsial diseases. The principle is based on serological cross reaction with antigens of three strains of Proteus – OX19, OX2 and OXK. The test had been around since World War I and has been

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faithfully used over the decades although it is neither sensitive nor specific. The “newer” tests like the indirect immunofluorescence (MIF) are more reliable but do not allow differentiation of infections among the Spotted Fever Group (SFG) rickettsiae. The IIP (indirect immunoperoxidase technique) has recently been introduced in Singapore and offers improved sensitivity and specificity. A commercially available ELISA dot assay (Dip-S-Ticks<sup>®</sup>) has been found to be comparable to the IIP for the diagnosis of murine typhus<sup>(7)</sup>. A high index of suspicion and clinical acumen continues to be extremely important in the diagnosis of rickettsial infection as serological confirmation may be delayed. Should empiric therapy be used as advocated by both authors<sup>(3,4)</sup>? An immigrant construction worker staying in a rat-infested container presenting with fever, headaches, cough or rash has a high likelihood of typhus fever and may be a candidate for empiric doxycycline therapy as suggested by the authors<sup>(3)</sup>. However, we cannot over-emphasise the importance of ruling out life-threatening diagnoses like meningitis, malaria and dengue fever, the latter two of which also have significant public health impact. Conversely, overuse of doxycycline may encourage development of resistance in Rickettsiae. A well known example is chloramphenicol in typhus treatment where increasing resistance is being reported due to overuse in developing countries.

Is typhus fever an emerging or re-emerging disease in Singapore or are we better able to diagnose it? Historical data from the time when typhus fever was a notifiable disease revealed that there were 84 cases reported over a nine-year period from 1968 to 1976<sup>(8)</sup>. In contrast, the two studies published in this issue had reported 41 serologically confirmed cases over varying periods from 1999 to 2000. While improved serological diagnosis may be an important factor, the numbers appear to warrant further epidemiological studies. Suffice to say that typhus has been with us for a long time and there is still a background level of disease activity locally. The other surprising epidemiologic piece of data has been the persistence of scrub typhus in Singapore, given the successful phasing out of scrub-land with the rapid urbanisation and industrialisation. There is still a fair disease burden in neighbouring countries and many of these cases could possibly be imported<sup>(9,10)</sup>. As stated by one of the authors, cross reactivity in the serological tests could account for false positive scrub typhus serology when in fact the clinical disease is more compatible with murine typhus rather than scrub typhus. In general, it would be true to say that murine typhus is still much more prevalent than scrub typhus in Singapore. In the clinical context, the treatment is the same.

The take-home message for local clinicians would be: Consider typhus in its differential diagnoses of patients with a PUO especially if it fits the risk group that is profiled in the two articles: a foreign migrant worker living in rat-infested or less than hygienic quarters and the traveller who had been to developing countries where the disease is still widely endemic. The Weil-Felix test is still not entirely obsolete but has to be interpreted in the correct clinical context. Empiric treatment has its place when life-threatening causes of fever have been excluded and the clinical assessment is compatible with typhus fever. The use of IIP is both sensitive and specific in helping to confirm or exclude the diagnosis.

For the scientist researcher, the field of rickettsioses is rapidly advancing and represents one of the best examples of the complementary roles of clinical medicine and laboratory techniques. **SMD**

*Is typhus fever an emerging or re-emerging disease in Singapore or are we better able to diagnose it?*

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