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Tropical respiratory medicine · 4

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Acute tropical infections and the lung

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Imported diseases are increasingly common and may present in many ways. A number of infections which are classically associated with non-pulmonary manifestations but which may cause acute pulmonary disease and thus present to chest physicians are described.

Falciparum malaria and respiratory failure

In severe *Plasmodium falciparum* malaria acute respiratory failure[1–5] may occur. It is relatively uncommon and generally the patient will have an additional complication such as cerebral malaria. Acute respiratory failure is rarely seen in African children, but is more common in south east Asian adults and non-immune whites. Characteristically it occurs 2–3 days into treatment when the peripheral parasitaemia is falling. It is heralded by the development of tachypnoea, orthopnoea, hypoxia, and cough. Inspiratory crackles and frothy sputum may be present, and the chest radiograph shows interstitial and alveolar oedema with a normal size heart (fig 1). In one series, seven of 11 patients with this complication of falciparum malaria died[5] despite aggressive treatment. Whilst frequently referred to in the literature as pulmonary oedema, the most detailed haemodynamic study[1] found the condition to be as prevalent in patients with severe falciparum malaria and normal pulmonary capillary wedge pressures as in those with elevated pulmonary pressures. There was no evidence from this study of left ventricular dysfunction, but hypoalbuminaemia and high parasitaemia were risk factors for the development of respiratory failure. Pathologically there is distension of the alveolar capillaries by pigment laden macrophages and inflammatory cells. Eosinophilic material is visible within the alveoli and this exudate may become organised with deposition of fibrin (fig 2). The appearances are similar to those of the adult respiratory distress syndrome (ARDS).

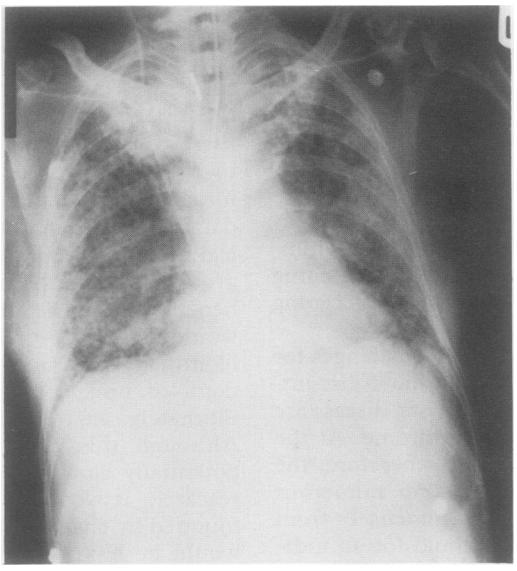

Figure 1 Chest radiograph showing bilateral interstitial infiltrates in falciparum malaria. Patient was receiving PEEP via an endotracheal tube, but the acute respiratory failure was eventually fatal.

In cerebral malaria the binding of infected red cells to postcapillary venule endothelium via a number of endothelial receptors is thought to be central to its pathogenesis.[6–10] Inflammation is unimportant. However, an ultrastructural study[10] showed some differences in the lung. The parasites seen in capillaries were almost all early trophozoite or ring forms, whereas late stages (schizonts and preschizonts) predominated in the brain. Other vessels contained large numbers of inflammatory cells including neutrophils, monocytes, and lymphocytes. In post capillary venules of the lung the Po_2 and pH are higher than in other organs and this does not favour parasite maturation. Red cells containing early ring stages of the parasite cannot deform in the normal way.[11] It is possible that such arrested parasites lodge in the pulmonary microvasculature and are relatively insensitive to treatment with drugs which are most effective against schizogony. The phenomenon of erythrocyte rosetting may contribute to the condition.[12] An inflammatory response to those parasites may develop and release mediators such as IL-6, platelet activating factor, and tumour necrosis factor, whose plasma levels are known to be raised in other forms of complicated malaria.[13–15] This may in turn lead to recruitment of more inflammatory cells with subsequent release of histiotoxic substances from neutrophils and macrophages leading to alveolar and endothelial damage.[16] Hypoalbuminaemia and therapeutic fluid overload will exacerbate the capillary leak. Some authors consider iatrogenic fluid overload itself to be central to the pathogenesis.[17] Further research on the molecular and cellular nature of this response, perhaps by in vivo determination of proteolytic enzyme and inflammatory cytokine levels in bronchoalveolar lavage,[18 19] would help to elucidate its true nature. The parasite

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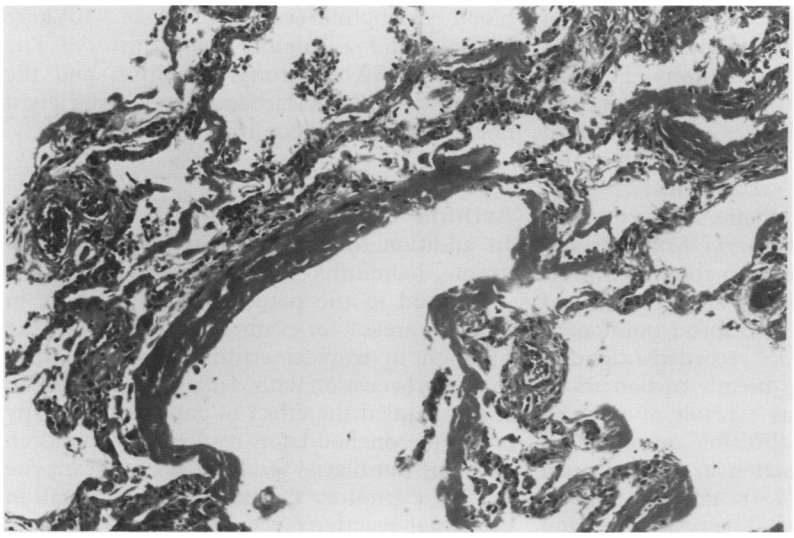

Figure 2 Postmortem histological section of the lungs of patient from fig 1 showing inflammatory infiltrate, thickened basement membrane, and eosinophilic exudate.

and host[20] determinants of this response could be investigated in vivo and in vitro.

The management of acute respiratory failure in falciparum malaria is difficult. Often the patient will be comatose, and may also have malarial haemoglobinuria (black water fever) and acute renal failure. Antimalarial drugs should be given at standard doses.[21] When respiratory failure is present (or any complication of falciparum, including vomiting, has supervened), intravenous therapy is mandatory; this should comprise a loading dose of quinine dihydrochloride 7 mg/kg (as the salt) over 30 minutes followed immediately by 10 mg/kg diluted in 10 ml/kg of isotonic fluid given over four hours and repeated every eight hours. If quinine is unavailable quinidine gluconate 10 mg/kg should be given as a loading dose over 1–2 hours followed by 0·02 mg/kg/minute for 72 hours. In either case the loading dose should be omitted if the patient has received quinine, quinidine, or mefloquine in the preceding 24 hours.[22] The patient should be intubated and ventilated early with positive end expiratory pressure.

Very high concentrations of inspired oxygen may be required to maintain arterial oxygen saturation. The haemoglobin should be maintained by blood transfusion, but it is important to avoid fluid overload. Monitoring of central venous pressure and pulmonary arterial pressure with flotation catheters provides useful information that must be interpreted in the knowledge that an exudative inflammatory process is occurring. Inotropic support is often necessary. Steroids are not proven to be of benefit in ARDS[16] and are known to be deleterious in cerebral malaria[23] which may coexist. The role of pulmonary vasodilators has not been systematically assessed; it is worth remembering, however, that the pulmonary vascular resistance in these cases is usually already decreased. The role of other anti-inflammatory treatments is not known. Further research on the detailed pathogenesis of this complication may lead to the identification of specific components of the inflammatory response that could be targeted in an attempt to reduce the high mortality.

Katayama fever

Schistosomiasis (bilharziasis) affects 200 million people worldwide and may produce systemic disease, including pulmonary disease, in its acute phase. Infection is acquired by exposure to schistosomal cercariae in fresh water. Penetration of cercariae through the skin is associated with itch in 70% of cases,[24] and occasionally with a papular rash (cercarial dermatitis). A seroconversion illness develops 3–6 weeks later, almost exclusively in non-immune visitors to endemic areas. The disease may vary from a mild malaise to a severe multisystem illness. In acute *S mansoni* and *S japonicum* infection (Katayama fever) pyrexia, malaise, backache, arthralgia, anorexia, urticaria, hepatosplenomegaly, cough, and the signs of a mild bronchitis are seen, with pulmonary symptoms in 33–65% of cases.[24 25] An eosinophilia of $0{\cdot}4–4{\cdot}0 \times 10^9/l$ is characteristic.[27] Although the acute phase of the disease is self limiting and not affected by antischistosomal therapy, diagnosis and treatment are important to avoid the sequelae of chronic infection. As the disease is a result of an immune reaction against schistosomal antigens around the time of early oviposition, standard screening using stool microscopy is unhelpful and the diagnosis is best made serologically – for example, by schistosomal enzyme linked immunosorbent assay (ELISA). Characteristically the antibody titre rises during the illness. Treatment for schistosomiasis is with praziquantel 40 mg/kg/day in divided doses for 1–3 days but, if given during the Katayama syndrome, clinical deterioration with exacerbation of symptoms due to hypersensitivity or the appearance of a condition similar to serum sickness may result. For this reason corticosteroids should be given in addition to praziquantel.[26] Praziquantel has little effect on immature worms so treatment should be repeated in patients whose last exposure was within the previous six weeks in whom the schistosomes may still be developing in their circulation. Schistosomiasis is focally distributed but is highly infectious and outbreaks of the Katayama syndrome have been reported in various groups of tourists returning from endemic areas, especially among those taking part in water sports.[25 27 28]

Helminths, eosinophilia, pneumonitis, and bronchospasm

Pulmonary eosinophilia resulting from parasitic infection may take the form of a mild illness with fever and cough that lasts for only a few days (Loeffler's syndrome). This is due to a transient allergic pneumonitis in response to parasite antigens during the invasive stage of larval migration of *Ascaris lumbricoides* (roundworms), *Ancylostoma duodenale*, and *Necator americanus* (both hookworms). Tropical pulmonary eosinophilia, however, pre-

sents with fever, cough, wheeze, lassitude, and weight loss. Hazy mottling is seen throughout the lung fields on chest radiography. The disease is found in countries where lymphatic (Bancroftian) filariasis is seen, particularly in children and young adults on the Indian subcontinent. It is seen in $<1\%$ of filarial infections and represents an inflammatory response to microfilariae of *Wuchereria bancrofti* and *Brugia malayi* that have been trapped in pulmonary capillaries. Several abnormalities of lung function are seen in tropical pulmonary eosinophilia. Vijayan *et al*[29] recorded a significant reduction in single breath carbon monoxide transfer (TLCO) as a result of reduced pulmonary membrane diffusing capacity that was itself due to a reduction in single breath alveolar volume (VA), pulmonary blood volume being unchanged. The restrictive lung defect significantly improved after treatment with diethylcarbamazine, while there was partial improvement FEV_1 and FVC.[30] In bronchoalveolar lavage fluid the total number of inflammatory cells (alveolar macrophages, lymphocytes, eosinophils, and neutrophils) correlated significantly with the reduction in TLCO and total lung capacity (TLC). The eosinophilia found in bronchoalveolar fluid was associated with a decline in TLCO but not FVC or TLC, whereas high alveolar macrophage and lymphocyte counts were associated with reduced lung volumes but not low TLCO,[31] suggesting that these different cell types might be associated with different mechanisms of lung damage. The pathogenesis of tropical pulmonary eosinophilia appears to be mediated by hypersensitivity to filarial antigens[32] but what predisposes certain individuals to develop the disease rather than classical filariasis is unknown. Analysis of IgE and IgG in bronchoalveolar lavage fluid revealed specificity against a restricted group of filaria specific antigens that were not detected in peripheral blood; it is thought that these antibodies are associated with destruction of microfilariae in the lungs.[33] Patients with tropical pulmonary eosinophilia show considerably increased circulating eosinophils and titres of microfilaria specific IgE,[34] but microfilariae are invariably absent from the peripheral blood.

By comparison, individuals with classical lymphatic filariasis have a degree of immunological tolerance and have large numbers of nocturnally periodic (in the case of *W bancrofti*) microfilariae, but less marked eosinophilia. An antigen from *B malayi* has been identified by two dimensional immunoblot analysis of pooled serum from patients with tropical pulmonary eosinophilia. The antigen expressed mainly in the microfilarial stage was capable of stimulating T cell mitogenesis and inducing IgE production in symptomatic patients. Furthermore, bronchoalveolar lavage fluid from these patients contained IgE antibodies that strongly recognised the same antigen.[35] The eosinophilia seen is probably T cell dependent. A diagnosis of tropical pulmonary eosinophilia is suggested by a characteristic chest radiograph, a very striking peripheral blood eosinophilia (counts of $10–25 \times 10^9/l$ are typical), and a suitable travel history. The filaria ELISA is strongly positive, and the response to diethylcarbamazine 200 mg eight hourly for 21 days confirms the diagnosis.

Asthma

In addition to their role in Loeffler's syndrome, helminths such as *Ascaris* have been implicated in the pathogenesis of asthma in endemic areas – for example, changes in airway function in tropical asthmatic patients may follow provocation with *Ascaris* extract. Lynch *et al*[36] studied the effect of antifilarial therapy on the bronchodilator response of children with positive filarial serology. A significant rise in peak expiratory flow rate (PEF) and fall in bronchial reactivity was seen after treatment with the broad spectrum antihelminthic pyrantel. In a study of atopic children with filariasis in Sri Lanka[37] treatment with diethylcarbamazine improved baseline PEF in all children with symptoms of asthma, and those with intermittent symptoms had a significant reduction in bronchial reactivity to histamine challenge.

It seems likely, therefore, that chronic helminth infections drive bronchoconstriction in susceptible individuals and could contribute to the progression of asthma in these children. It is not clear if helminths actually trigger asthmatic attacks. Such attacks would be related to a type 1 hypersensitivity reaction mediated by antihelminth IgE, which is found in the sera of these patients, when challenged with these antigens. Paradoxically, in other studies helminth infections have been associated with the suppression of allergic responses to environmental allergens in endemic areas.[38 39]

Typhoid fever

Respiratory symptoms are common in *Salmonella typhi* infections, being present in about half of the cases at the onset of the disease. In one series 8% of typhoid cases had an initial diagnosis of respiratory infection.[40] Chills, malaise, anorexia, and headache are almost universal. During the course of the disease coryza (60%), cough (86%), crackles (64%), chest pain (60%), and pleural effusion (0·5%) were seen in a series of 360 cases.[40] In this study 37 of the 154 patients who had a chest radiograph showed radiological signs of bronchopneumonia; 18 also had hilar enlargement or peribronchial thickening.

Evidence that *S typhi* is the aetiological agent of pneumonia in typhoid fever is scanty. Three cases of pneumonia in serologically proven cases of typhoid fever were found to show no secondary pathogen and to respond to treatment for typhoid.[40–42] *S typhi* has been found in the sputum of one patient[40] and isolated from consolidated lungs at postmortem examination. In cases of typhoid pneumonia ciprofloxacin is likely to be curative. In advanced typhoid, however, secondary bacterial pneumonia is common and may be due to aspiration or to another pathogen such as *Staphylococcus*

aureus. This serious complication is more common in the elderly and in those with underlying diseases such as malignancy, diabetes mellitus, or pre-existing pulmonary disease. *S typhi* bacteraemia may seed at any site and lung abscess and secondary infection in pleural effusions may ensue. Abscess formation may be indicated by failure to defervesce on treatment and by a rising neutrophil count.[43] Typhoid is best diagnosed by taking (at least) three sets of blood cultures and a stool culture before starting antibiotics. Serological examinations, such as the Widal test, are often confounded by prior salmonella infections or typhoid immunisation.

Scrub typhus

Tsutsugamushi fever, or scrub typhus, is an acute febrile illness in which respiratory abnormalities are common. The aetiological agent, *Rickettsia tsutsugamushi*, is an obligate intracellular bacterium endemic in the region stretching from Pakistan to Japan and northern Australasia, including India and south east Asia. The infection is zoonotic, the reservoir being the wild rat. The vectors are trombiculid mites. In areas where low level vegetation allows man, the rat, and the chigger (the larval form of the mite) to coexist, infectivity is high. Two days after the bite of an infected chigger a papule may form at the site of inoculation and will evolve into an ulcer with a black necrotic centre, the eschar of which is an important clue to diagnosis. Classically, over the following five days regional, then generalised, lymphadenopathy will develop. Six to eight days after inoculation a generalised maculopapular rash develops. Fever and headache are invariable. Cough, often severe and non-productive, was recorded in 45% of cases in one series.[44] Careful search reveals an eschar in half the cases only, and a rash in one third.[44] Splenomegaly is common. Signs of respiratory disease are scanty but radiographs may reveal evidence of interstitial pneumonitis. This complication is due to, and part of, a generalised vasculitis and is found in almost all fatal cases of the disease.[45] It is not as common in scrub typhus, however, as it is in classical epidemic or louse borne typhus. In the endemic area of scrub typhus 20% of all febrile patients in hospital may have *R tsutsugamushi* infection.[46] Sometimes the disease presents only with chest signs – for example, as interstitial pneumonitis with lower lobe pneumonia or pleural effusions. A raised neutrophil count is usually seen.[47] Diagnosis is confirmed by a rising titre of antibodies in paired sera – for example, by immunofluorescence against *R tsutsugamushi* which is more sensitive than the Weil-Felix test.[48] Treatment is with tetracyclines or chloramphenicol, and a single dose of 200 mg doxycycline is effective. Before specific chemotherapy became available, mortality from the disease ranged from 5–30%.[45]

Strongyloidiasis

A severe respiratory infection of increasing importance is hyperinfection with *Strongyloides stercoralis*, a free living and parasitic nematode that is endemic throughout the tropics. The most common respiratory manifestation of *S stercoralis* infection in normal hosts is Loeffler's syndrome, presenting as transient cough and wheeze, during the migration of the infective larvae through the lungs.

Hyperinfection is seen in the immunocompromised patient when larvae that have hatched from eggs laid by adult worms in the duodenum and jejunum develop into the infective stage, repenetrate the bowel wall, and develop into adult worms. A very heavy infection ensues and larvae spread throughout the body, especially into the lungs. The patient at first may be asymptomatic, but soon presents with progressive respiratory disease, weakness, malaise, weight loss, symptoms of malabsorption, and a serpiginous or linear and rapidly migrating urticarial eruption (lava currens). Other organs including the brain may be involved. The respiratory syndrome may resemble ARDS.[49] Larvae are present in sputum, urine, stool, and many tissues. Gram negative faecal flora, travelling with the larvae, may cause meningitis, pneumonia, or septicaemia. Radiographically, diffuse or segmental infiltrates are seen. The striking peripheral eosinophilia of migrating parasitic infections is usually absent during hyperinfection because of the underlying defect in cell mediated immunity. The disease is seen in association with steroid dependence in chronic bronchitics,[50] following renal transplantation where a 50% mortality is seen,[51] specifically in HTLV 1 infection,[52] and in several other immunosuppressive states, but surprisingly rarely in HIV infection and AIDS. The clinical features alone seldom permit a diagnosis but history of travel to an endemic area, even in the distant past,[53] in an immunosuppressed patient with rapidly progressive multisystem involvement is usual. The index of suspicion should be greater in those of Caribbean or West African origin. Unfortunately it is not uncommon for this diagnosis to be made after death.[54] In a suspected case the stool should be examined for the larvae by a concentration technique and the sputum and urine should be examined microscopically. Duodenal larvae are collected by a string test in which a gelatin capsule is swallowed attached to a fluffy nylon thread; after several hours the string is retrieved and the attached mucus is examined microscopically for larvae. *Strongyloides* ELISA is a useful serological test. Treatment is with thiabendazole or albendazole.[55] Albendazole is less toxic, and an adult dose of 400 mg 12 hourly, through a nasogastric tube if necessary, for at least 14 days may be the best treatment option at present. There is no parenteral preparation. After recovery the patient should be screened for persistent infection by repeated stool examinations for larvae and by serological tests.

Conclusion

Successful management of exotic tropical and parasitic infections requires a familiarity with

the organisms, their life cycles, their clinical spectrum and associated risks, and also with the appropriate methods of diagnosis and treatment. Chest physicians who suspect such infections should seek help from their clinical colleagues in infectious and tropical diseases at an early stage.

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