Occasional reviews

Erythromycin and diffuse panbronchiolitis

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Diffuse panbronchiolitis (DPB) was first described by Yamanaka as a distinct clinicopathological entity almost three decades ago.[1 2] The histological features characteristic of DPB are chronic inflammation localised mainly in the respiratory bronchioles and adjacent centrilobular regions with infiltration of plasma cells and lymphocytes. Formation of lymphoid follicles is occasionally observed. Small conducting airways sometimes show luminal stenosis or dilation with subepithelial infiltration of plasma cells and lymphocytes, and fibrotic and elastolytic lesions. Foamy cells accumulate in the wall of respiratory bronchioles, adjacent alveolar ducts, and alveoli with infiltration of lymphoid cells (unit lesions of panbronchiolitis[3]). These lesions affect both lungs diffusely. The chronic inflammatory lesions often extend to the more proximal bronchioles, leading to secondary bronchiectasis observed in the advanced stages. Thus, diffuse bronchiectasis is one of the most important differential diagnoses, in which case major lesions are found in the region of conducting airways and foamy cells rarely accumulate in the pulmonary interstitium. No significant lesions are normally found in the alveolar areas away from the centrilobular lesions.

The clinical presentation is characterised by chronic cough with mucopurulent sputum, exertional dyspnoea, and disseminated reticulonodular densities on the chest radiograph, predominantly in the lower lung fields, with hyperinflation of the lungs. The appearance on high resolution computed tomographic scanning is characteristic and is helpful in pointing to the diagnosis; the major findings include small rounded areas of attenuation with a centrilobular distribution, branching linear areas of attenuation, and hypoattenuation in the peripheral lung.[4] Typical abnormalities in lung function are an obstructive and/or restrictive defect; this chronic airflow limitation is more resistant to bronchodilators than that of chronic obstructive pulmonary disease.[5]

The disease has been reported to be more prevalent in men and most have never smoked. The peak incidence occurs in the fifth and sixth decades,[6] though it can occur at any age of adult life.[7] The titre of the cold haemagglutinin is raised in most patients,[8] and the changes in the titre reflect the therapeutic response to some extent. Other laboratory abnormalities include raised erythrocyte sedimentation rate, positive C reactive protein (CRP) and positive rheumatoid factor (40%).[9] Early in the course of the disease sputum culture is often positive for *Haemophilus influenzae*; in many cases this is replaced by *Pseudomonas aeruginosa* in the advanced stage.

Before the advent of erythromycin therapy the prognosis of the disease was dismal; the 10 year survival from the onset of dyspnoea was 73.1–78.1% in cases without *P aeruginosa* infection and 12.4–21.9% for those with *P aeruginosa* infection. Corticosteroids had been employed empirically without significant success in improving morbidity and mortality. Although no reliable statistics are available, many respiratory physicians agree that the incidence of the disease is now on the decline. This was partly supported by the second national survey conducted in 1988 by the Ministry of Health and Welfare of Japan in which 26 institutes all over Japan took part. Chronic sinusitis is almost always found in patients with DPB, leading to the concept that DPB is part of a disease spectrum called sinobronchial syndrome. In addition, it has been suggested that clinically diagnosed DPB includes cases with, not only pathological DPB, but also unclassified bronchiolitis and bronchiolectasis.[10] Conversely, some cases with typical pathological findings of DPB do not fulfil the clinical diagnostic criteria.[11] Thus, patients with clinically diagnosed DPB do not necessarily have the typical pathological findings of DPB and may include cases with non-specific diffuse bronchiectasis; many of the studies reviewed here have been based on these clinically diagnosed patients.

DPB is not uncommon in Japan, but is rare elsewhere. There have been a few case reports from outside Japan involving non-Japanese patients.[3 12-18] A small number of patients have also been confirmed in Korea and Taiwan.[10] Intriguingly, Sugiyama and associates reported the increased incidence of HLA-Bw54 in patients with DPB,[19] this allele being rare except in Japanese, Chinese, and Korean populations and thus suggesting some genetic component to the disease. However, this association is yet to be confirmed. In addition, a relatively small number of familial cases has been reported thus far,[20] though it is not unusual that some of the siblings of the patients have chronic sinusitis without chest lesions.

Based on a detailed observation of a single case, Kudoh *et al* noticed that erythromycin might be effective in treating patients with DPB and performed an open trial which showed the beneficial effect of low dose, long term treatment with erythromycin (400–600 mg for

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at least six months) on DPB.[21] This favourable effect was observed even in patients with *P aeruginosa* infection[22–24] and those with chronic respiratory failure.[25] The long term administration of erythromycin was not associated with the replacement of *H influenzae* by *P aeruginosa*.[21 26] Some of these effects were later confirmed by a placebo controlled, double blind clinical trial.[27] These observations have been further extended to diffuse bronchiectasis associated with chronic sinusitis by several uncontrolled studies.[23 26] Subsequently, other macrolide antibiotics including clarithromycin,[28] roxithromycin,[29] and azithromycin[30] were also reported to be effective.

The effectiveness of erythromycin in DPB seems to be due to mechanisms other than antibacterial activity, because the maximum serum and sputum levels of erythromycin in this dosage were below the minimum inhibitory concentrations for *H influenzae* and *P aeruginosa*.[24] This is also supported by the observation that the bacteria in the sputum were not always eradicated in the erythromycin responsive patients.[24] In addition, a patient with recurrent DPB after bilateral lung transplantation was successfully treated with erythromycin without any change in immunosuppressive treatment,[15] supporting the specific effect of erythromycin on DPB. Furthermore, erythromycin was shown to be more effective than fluoroquinolones in treating patients with DPB in a retrospective analysis,[31] suggesting that antibacterial activity is not the only determinant of the efficacy of erythromycin. Based on these observations, many hypotheses have been advanced as to the mechanism of the effect of erythromycin on DPB. Here we will review briefly the studies in this field.

As marked neutrophilia is a prominent feature of the bronchoalveolar lavage (BAL) fluid in patients with DPB, much of the work has been focused on the effect of erythromycin on neutrophil function, though conflicting results have been reported regarding the effects of the drug on neutrophil migration, chemotaxis, and generation of reactive oxygen species. However, a substantial decrease in the number of neutrophils in the BAL fluid from patients with DPB is observed during treatment with erythromycin.[32 33] In keeping with this, erythromycin has been shown to suppress the neutrophil influx into the alveoli in response to challenge with *Proteus mirabilis*[34] or IL-8.[35]

Oishi *et al* showed an increase in the IL-8/albumin ratio in the BAL fluid from patients with chronic *P aeruginosa* infection as well as a significant reduction in this ratio with erythromycin treatment. They also demonstrated in vitro that erythromycin suppressed *Pseudomonas* induced, neutrophil derived IL-8 in a dose dependent manner, but did not suppress IL-1β induced IL-8 production.[36] They concluded that persistent *Pseudomonas* infection enhances IL-8 production leading to neutrophil accumulation in the airways, and erythromycin might exert its effect through suppression of IL-8 production. Although there are conflicting data on the in vitro effect of erythromycin on TNF-α and IL-1 production by human mononuclear cells or whole blood stimulated by lipopolysaccharide,[37–40] a significant reduction has been observed in IL-1β and IL-8 in parallel with neutrophils in the BAL fluid from patients with DPB after erythromycin treatment,[41 42] suggesting a possible role for these cytokines in the pathogenesis of DPB and the effect of erythromycin on them. A reduction in leukotriene B_4 in BAL fluid was also shown to correlate with the decrease in neutrophils.[43]

Aoshiba and associates reported that erythromycin accelerated apoptosis of cultured neutrophils in a dose dependent manner. Apoptotic neutrophils, unlike necrotic cells, retain their membrane integrity and are efficiently phagocytosed by macrophages without releasing histotoxic contents, thus erythromycin may limit tissue injury.[44] An increased level of defensins was also reported in the BAL fluid from patients with DPB which was significantly reduced by treatment with macrolide antibiotics. A strong immunoreactivity for defensins in neutrophils and mucinous exudates in the airways and in the surface of bronchiolar epithelial cells in open lung biopsy specimens was shown in patients with DPB, and the authors suggested that the lung injury in DPB could be caused by the accumulation in the airways of defensins released by neutrophils.[45] On the other hand, pretreatment with erythromycin failed to suppress the induction of expression of the adhesion molecules, MAC-1 and LFA-1, on neutrophils drawn from healthy volunteers in vitro.[46]

Although erythromycin lacks bacteriostatic or bactericidal activity against *P aeruginosa*, some possible interactions between the drug and *P aeruginosa* have been reported. Kadota *et al* demonstrated that *P aeruginosa* exposed to erythromycin was more susceptible to the bactericidal activity of polymorphonuclear leucocytes, possibly by increasing the bacterial susceptibility to the neutrophil oxygen dependent killing mechanism.[47] Yamasaki showed a significant reduction in the number of pili per bacterium in the piliated *P aeruginosa* grown in a media containing subminimal inhibitory concentrations of erythromycin, minocycline and clindamycin, as well as a decrease in the adherence of the bacteria treated with erythromycin to the acid injured tracheal epithelium of mice in parallel with the reduction in piliation.[48] In addition, several investigators have shown that macrolides inhibit elastase production by *P aeruginosa* without affecting the bacterial proliferation.[49 50] Such exoproduct elastase may be responsible for the tissue damage in DPB. Furthermore, relatively low concentrations of clarithromycin have been shown to interfere with the formation of biofilm by *P aeruginosa*,[51 52] resulting in a synergistic effect with fluoroquinolones on *P aeruginosa* infection. This interference was associated with a decrease in the amounts of alginate and hexose.[52]

The effects of erythromycin on lymphocytes have also been investigated because lymphocyte accumulation around respiratory bronchioles is a striking pathological feature of the disease.[2 53] Sugiyama and associates found increased per-

centages of activated CD8+, CD4+, and CD3+ cells in peripheral blood drawn from patients with DPB and showed that treatment with erythromycin – but not fluoroquinolones – resulted in a decrease in the percentages of these cells.[54] Using an animal model of chronic respiratory *P aeruginosa* infection in which mice were intubated with a tube precoated with *P aeruginosa*, Yanagihara *et al* demonstrated a decreased CD4+/CD8+ ratio in the lungs which was reversed by clarithromycin treatment without any changes in the number of bacteria; ofloxacin reduced the number of bacteria but did not influence the ratio.[55] This change in the CD4+/CD8+ ratio was consistent with the observation in patients with DPB who have been treated with erythromycin.[56] Taken together, erythromycin may well modulate the lymphocyte function and thus affect the disease process without a significant influence on the bacteria. In addition, erythromycin has been shown to suppress a mitogen mediated lymphocyte proliferative response.[57 58] A significant increase in natural killer cell activity in the blood of patients with chronic lower respiratory tract infection after erythromycin treatment has also been reported; this increase preceded the clinical improvement.[59]

Because the production of quantities of sputum is one of the main clinical manifestations of DPB, the effect of erythromycin on bronchial secretion may be another possible mechanism of its action. Goswani and associates showed that erythromycin inhibited respiratory glycoprotein secretion by human airways in a dose dependent manner in vitro.[60] Tamaoki *et al* reported that the addition of erythromycin to the submucosal side of cultured canine tracheal epithelium decreased a short circuit current in a dose dependent manner and attributed this to the inhibition of chloride secretion across the airway epithelium.[61] They also reported the inhibition of IL-8 induced goblet cell secretion by treatment with macrolides in guinea pigs.[62] These observations may explain the drying effect of erythromycin in various diseases including DPB.

Despite the passage of nearly three decades since the first description of DPB, the aetiology of the disease remains obscure. In addition, a more inclusive terminology such as sinobronchial syndrome may be more appropriate for cases without a pathological diagnosis. Nevertheless, the beneficial effects of erythromycin treatment have changed the outlook for the disease and many studies are underway to elucidate the mechanism of its action. It is to be hoped that these studies will lead to a new therapeutic approach to DPB and/or an extended application of this treatment to other similar conditions.

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