Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Carbamazepine-induced agammaglobulinaemia clinically mimicking diffuse panbronchiolitis

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Summary

The authors report the case of a 61-year-old man who presented with carbamazepine (CBZ)-related agammaglobulinaemia accompanied by sinobronchial syndrome clinically mimicking diffuse panbronchiolitis (DPB). The patient's laboratory and radiographic findings improved significantly after cessation of CBZ, and administration of gammaglobulin and long-term oral macrolides therapy. In patients on long-term CBZ treatment, the physician should be aware of the possible development of secondary immunodeficiency, which can cause small airway diseases sharing common clinical features with DPB.

BACKGROUND

Diffuse panbronchiolitis (DPB) is an idiopathic inflammatory disease, which, left untreated, progresses to bronchiectasis, respiratory failure and cor pulmonale, resulting in poor prognosis.¹ The clinicopathological features, the coexisting sinusitis and the isolation of *Haemophilus influenzae* in the sputum enhance disease recognition.² This condition is well recognised in Japan, while uncommon in western countries.² Genetic, environmental and immunological factors are believed to play key roles in the development of DPB.²

Carbamazepine (CBZ), widely used to treat epilepsy and neuropathic pain, has been implicated as causing a variety of immunological abnormalities.^{3–9} We present a case with sinobronchial syndrome associated with CBZ-induced agammaglobulinaemia, sharing common clinical features with DPB. The possible pathogenesis, diagnosis and management are discussed.

CASE PRESENTATION

A 61-year-old man was admitted to our hospital with a 3-month history of exertional dyspnoea and productive cough. He had no congenital or inherited disorders including immunodeficiency and no history of smoking. He had undergone removal of a meningioma in the right temporal lobe and surgical debridement for a postoperative epidural abscess 2 years previously. Since having several seizures secondary to meningioma perioperatively, the patient had been taking CBZ with excellent seizure control and no predictable adverse reactions. On admission, his blood pressure was 136/67 mm Hg, his pulse was 110/min and his temperature was 38.3 °C. Chest auscultation revealed coarse crackles over both lung fields.

INVESTIGATIONS

On laboratory findings, the serum immunoglobulins (Ig) were markedly decreased (IgG 46 mg/dl, IgA <5 mg/dl, IgM <5 mg/dl). In peripheral blood, the white cell count

was normal while lymphocyte surface markers showed complete absence of CD19 B lymphocytes with CD4 T lymphopaenia of 439/ μ l and an inverted CD4:CD8 ratio of 0.3. The blood concentration of CBZ was within the therapeutic range. Bone marrow examination showed absence of CD138 plasma cells. The level of serum cold agglutinins and rheumatoid factor were normal. The purified protein derivative skin test was negative. Pulmonary high-resolution CT (HRCT) revealed diffuse centrilobular nodules connected to distal branching bronchovascular structures, which has a tree-in-bud appearance without the presence of thymoma (figure 1). On brain CT, maxillary sinusitis was noted without recurrence of the epidural abscess. *H influenzae* was isolated from sputum cultures, while mycobacterial cultures and blood cultures exhibited no growth. Arterial blood gas analysis demonstrated PO₂ 74.6 mm Hg and PCO₂ 37.4 mm Hg. Pulmonary function testing revealed an obstructive pattern with a forced expiratory volume in 1 s/forced vital capacity of 65%. On bronchoscopy, bronchoalveolar lavage revealed neither *Pneumocystis jiroveci* nor *Aspergillus fumigatus* pathogens. However, transbronchial biopsy unfortunately yielded no specific findings because the amount of tissue obtained was insufficient to diagnose DPB.

TREATMENT

The patient was clinically diagnosed as having DPB as he fulfilled the diagnostic criteria laid down in 1998 by a working group of the Ministry of Health and Welfare of Japan¹⁰ (Table 1). Sodium valproate was substituted for CBZ, which was the most likely cause of the agammaglobulinaemia, based on past history and clinical findings. The patient's fever had abated by the 8th hospital day as a result of 10-day administration of cefotaxime 4 g/day (1 g every 6 h) with gammaglobulin supplementation to maintain the serum IgG level above 500 mg/dl. Long-term oral clarithromycin 400 mg/day (200 mg every 12 h) was initiated after cessation of cefotaxime. After discharge on

Figure 1 High-resolution computed tomography reveals multiple centrilobular nodules connected to distal branching bronchovascular structures, presenting a tree-in-bud appearance without the presence of thymoma.

Table 1 Diagnostic criteria for diffuse panbronchiolitis

1. Persistent cough, sputum and exertional dyspnoea.
2. Coexistence or history of chronic paranasal sinusitis.
3. Bilateral diffuse small nodular shadows on a plain chest radiography or centrilobular micronodules on chest CT.
4. Coarse crackles on auscultation of the chest.
5. FEV1/FVC $\leq 70\%$ on pulmonary function tests and PaO₂ ≤ 80 mm Hg on blood gas analysis.
6. Elevated titres of cold haemagglutinin: $\times 4$ and more.

Cases definitely diagnosis should fulfil criteria 1, 2 and 3, along with at least two of criteria 4, 5 and 6. The present case fulfilled criteria 1, 2, 3, 4 and 5
1 mm Hg = 0.133 kPa

FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PaO₂, arterial oxygen tension.

the 28th hospital day, intravenous gammaglobulin supplementation was continued every 2 weeks with no further infectious complications.

OUTCOME AND FOLLOW-UP

The serum IgG level normalized even without further gammaglobulin supplementation, while the IgM and IgA levels remained low 5 months after cessation of CBZ. Respiratory symptoms subsided with resolution of the HRCT findings 6 months after cessation of CBZ (figure 2). The patient is currently receiving a 2-year course of clarithromycin.

DISCUSSION

Patients with humoral immunodeficiency often develop small airway diseases. In a report on CT findings, adult patients with primary immunodeficiency were at increased risk of a wide spectrum of pulmonary lesions.¹¹ According to this report, 47% of patients with B cell disorders had small airway diseases such as centrilobular lesions or bronchiectasis,¹¹ sharing the same or similar radiographical feature with DPB. Patients with a B cell immune deficiency are susceptible to infection by encapsulated bacteria such

as *Haemophilus* species.¹¹ Early stage DPB is also often associated with *H influenza* infection, while in the advanced stage, colonisation or infection with *Pseudomonas aeruginosa* can accelerate the destructive process, leading to diffuse bronchiectasis and cystic changes in the lungs.²

In the present case, humoral immunodeficiency could have increased susceptibility to the *H influenza* infection responsible for inflammation centred on the respiratory bronchiole and adjacent centrilobular regions.

Although the association of CBZ with the immune system is less well established, CBZ has been implicated in a variety of immunodeficiency disorders such as agranulocytosis or neutropaenia,³ immunosuppressant effects on T cells,⁴ absence of B cells,⁵ a disorder of the class-switch from IgM+B cells to IgG+B cells,⁶ impairment of the synthesis of immunoglobulins in B cells,⁷ monoclonal gammopathy of undetermined significance⁸ and reduced serum IgA and IgM with normal numbers of T or B lymphocytes.⁹

The present case had combined B and T cell immunodeficiency, as found in patients with hypogammaglobulinaemia with thymoma (Good's syndrome), characterised by few or absent B cells, an abnormal CD4:CD8 T cell ratio,

Figure 2 High-resolution computed tomography 6 months after the cessation of carbamazepine treatment reveals the resolution of the centrilobular lesions.

CD4 T cell lymphopaenia and impaired T cell mitogenic responses.¹² In Good's syndrome, recurrent sinopulmonary infections secondary to encapsulated organisms are the most common infectious diseases,¹³ while only a few cases of DPB with excellent response to macrolides therapy have so far been described in relation to Good's syndrome,¹⁴ presumably because of lack of familiarity with DPB. In addition, a bare lymphocyte syndrome, characterised by immunodeficiency due to defective antigen processing, has been described as having close similarity to the DPB phenotype and being successfully treated with macrolides therapy.¹⁵

A diagnosis of DPB is made by demonstrating its distinctive features. Surgical lung biopsy is generally recommended to confirm a definite diagnosis in countries where DPB is very rare, but is unnecessary where the disease is prevalent. According to the Japanese diagnostic criteria described above (table 1),¹⁰ histopathology is not mandatory for a definite diagnosis of DPB.

In DPB, long-term treatment with macrolide antibiotics improves symptoms,¹⁶ radiological findings¹⁶ and survival rates.¹ The beneficial effect of macrolides may be due not to antibacterial but to anti-inflammatory and immunoregulatory actions.² Both clarithromycin and erythromycin are 14-ring macrolides widely used in the treatment of DPB.² The optimal duration of macrolides therapy is not unknown, but in Japan most patients are treated for 6–24 months. According to Japanese clinical guideline for DPB,¹⁰ the duration of treatment should be at least 6 months with follow-up assessment of overall response and be completed after 2 years provided clinical manifestations, radiological findings and pulmonary function measurements improve and stabilise.

Despite the clinical diagnosis of DPB, the present case probably should be distinguished from usual DPB because it occurred in the presence of an underlying immunodeficiency, which is inconsistent with the typical laboratory features seen in many DPB patients including increased serum cold agglutinins and increased serum IgA and IgG levels.¹⁷ However, it was shown that long-term macrolides therapy might be a therapeutic option for even the immunodeficient patient clinically presenting as DPB.

According to previous reports, it takes at least several months before recovery of immunological abnormalities begins following withdrawal of CBZ^{6 8} and administration of gammaglobulin to maintain IgG values above 500 mg/dl to reduce the recurrence of infections.¹⁸ In the present case, recovery of serum Ig levels began 6 months after the withdrawal of CBZ and during the convalescent period,

Learning points

- ▶ In patients on long-term carbamazepine therapy, the physician should monitor Ig serum levels and the lymphocyte subpopulation.
- ▶ Patients with humoral immunodeficiency often develop small airway diseases or sinobronchial syndrome.
- ▶ In patients with small airway diseases or sinobronchial syndrome, diffuse panbronchiolitis should be considered in the differential diagnosis.
- ▶ In patients with humoral immunodeficiency clinically diagnosed as diffuse panbronchiolitis, long-term macrolides therapy should be a therapeutic option as well as gammaglobulin supplementation.

and gammaglobulin supplementation as well as long-term macrolides may have significantly reduced the frequency and severity of the pulmonary infection,¹⁹ resulting in the favourable clinical course.

Competing interests None.

Patient consent Obtained.

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