CASE REPORT

Granulomatous-lymphocytic interstitial lung disease and recurrent sinopulmonary infections in a patient with Good's syndrome

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SUMMARY

Good's syndrome is a rare primary immunodeficiency associated with adult thymoma. Complications are mainly autoimmune manifestations and recurrent infections with encapsulated bacteria. Only one possible case of combined granulomatous-lymphocytic interstitial lung disease (GL-ILD) and Good's syndrome have been described earlier, but the patient died at the time of diagnosis. This is the first case of GL-ILD in Good's syndrome with a successful outcome. We present a case of a 43-year-old man with GL-ILD, who suffered from recurrent infections of *Haemophilus influenzae* and *Pneumocystis jirovecii*, with 8-year follow-up. After a thymectomy, he was diagnosed with Good's syndrome and GL-ILD. He was treated with prophylactic pivampicillin, quinolones and cephalosporins for his recurrent *P. jirovecii* and *H. influenzae* infections, an approach that proved unsuccessful due to resistance, with relapse after cessation. He was stabilised with oral diaminodiphenyl-sulfone for *P. jirovecii* and colistimethate-sodium inhalations for *H. influenzae*, which is a new approach to prophylactic treatment.

BACKGROUND

Good's syndrome is defined as a combination of adult onset hypogammaglobulinaemia, thymoma, low or absent B cells and variable defects in cell-mediated immunity.^{1 2} A defective humoral immunity is thought to be present as well, accounting for the recurrent sinopulmonary infections with encapsulated bacteria.^{1 2} Since its discovery in 1954, only 243 cases have been reported. Similarly to common variable immunodeficiency (CVID), Good's syndrome is defined as an independent primary immunodeficiency by the WHO. It differs from CVID by the low or absent B cell count and thymoma and is associated with a markedly increased mortality.¹ The mean age at diagnosis is 59 (40–70); CVID starts in early adolescence or childhood.¹ Hypogammaglobulinaemia can be found in 3–10% of patients with adult thymomas, and a considerable number of these patients are thought to have Good's syndrome.^{1–3}

The most common complications are recurrent infections, diarrhoea and autoimmune manifestations. As in other primary immunodeficiencies, infections are mostly located in the sinopulmonary system where encapsulated bacteria such as *Haemophilus influenzae*, *Klebsiella* spp, *Streptococcus pneumoniae* as well as *Pseudomonas* spp are the most common pathogens.

Opportunistic infections with cytomegalovirus, *Candida* spp, herpes virus and *Pneumocystis* spp have also been reported and are thought to be caused by defects in the cell-mediated immunity.^{1 2} Currently, there is no consensus regarding prophylactic antibiotic treatment. The reported average follow-up is only 1.7 years in the 70 case reports that provide information on follow-up.^{1–2 4}

A total of 90/153 (59%) patients have autoimmune complications such as pure red cell aplasia, myasthenia gravis and a spectrum of other haematological and endocrinological manifestations.^{1 2} However, only one possible but unconfirmed case of concomitant granulomatous-lymphocytic interstitial lung disease (GL-ILD) and Good's syndrome has been reported.⁴

We present a case of a 43-year-old man with Good's syndrome and GL-ILD, with recurring infections of *H. influenzae* and *Pneumocystis jirovecii*, through a follow-up period of 8 years. The patient was stabilised with inhaled colistimethate-sodium for *H. influenzae* and diaminodiphenyl-sulfone for *P. jirovecii*, the former being a new approach to prophylactic treatment for *H. influenzae*.

CASE PRESENTATION

A healthy 43-year-old man was, in 2005, admitted to his local hospital because of increasing dyspnoea during the past 6 months, reduced appetite and a 22 kg weight loss. He had never been a smoker and had no recurrent infections. Spirometry was normal. CT of the thorax revealed a mediastinal mass compatible with a thymoma (figure 1). Surgery was performed and histopathology found a benign thymoma type AB. After surgery, all symptoms subsided and the patient was discharged without further treatment.

Three months later, the patient was readmitted with dyspnoea and restrictive lung function decline. High-resolution CT (HRCT) showed extensive ground glass opacities, centrilobular nodules and

Figure 1 CT and chest X-ray with anterior mediastinal mass compatible with thymoma (*).

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Table 1 Laboratory findings on admission in 2006

IgG	19 µmol/L (41–99)
IgA	1.5 µmol/L (4.8–24)
IgM	<0.11 µmol/L (0.41–2.19)
Total leucocytes	8.5×10 ⁹ /L (3.5–10)
Total lymphocytes	0.9×10 ⁹ /L (1.3–3.5)
CD3 positive	0.85×10 ⁹ /L (55–83%) 98% of total lymphocytes
CD3 negative	0.05×10⁹/L (16–45%) 2% of total lymphocytes
CD4+	0.41×10 ⁹ /L (>0.4–0.5) Later dropped to 0.28×10 ⁹ /L
CD8+	0.42×10 ⁹ /L (0.21–0.88)
CD4/CD8 ratio	0.41/0.42=1.0
ANCA	Negative
ANA	Negative
ACE	Negative
HIV	Negative

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody.

enlarged mediastinal lymph nodes. Desquamative interstitial pneumonia or hypersensitivity pneumonitis was suspected and he was referred to the Department of Respiratory Medicine, Aarhus University Hospital.

INVESTIGATIONS

At admission, lung auscultation revealed fine crackles but no drumstick fingers or hour-glass nails were observed. A 6 min walking test showed desaturation to 69%.

Pulmonary function tests (PFT) confirmed the restrictive pattern with forced expiratory volume in 1 s (FEV₁) 2.5 L (54% of predicted), forced vital capacity (FVC) 2.76 (49%), FEV₁/FVC 90%, total lung capacity (TLC) 52% of predicted and diffusion capacity for carbon monoxide (TLCO) 34% of predicted. Immunoglobulins and peripheral B cells were low combined with a low CD4/CD8 ratio (table 1).

Bronchoscopy with bronchoalveolar lavage fluid (BAL) showed inflammation with numerous lymphocytes and low CD4/8 ratio. No pathogens were found. Owing to the suspicion of interstitial lung disease, a diagnostic surgical lung biopsy was performed, showing loose, non-necrotising granulomas, some with giant cells, and also peribronchial chronic inflammation (figure 2). No fibroblast foci, fibrosis, signs of *P. jirovecii* or tuberculosis were found and the biopsy was thus found compatible with GLILD.

TREATMENT

The patient was started on oral prednisolone 50 mg once a day and subcutaneous human immunoglobulin (Subcuvia) 3200 mg, five times a week, with an intended P-IgG-level of 7 g/L, resulting in improved PFT and malaise; however, dyspnoea persisted. CD4 count was above 200 cells/µL, hence pneumocystis prophylaxis was not initiated.

OUTCOME AND FOLLOW-UP

Two months later, the patient reported of increasing dyspnoea; a productive cough and decrease in PFT were noted. IgG count was normal and HRCT showed almost complete regression of the ground glass opacities. The patient had a low CD4 count of 280 cells/µL. BAL culture found *P. jirovecii* as well as *H. influenzae*, and prednisolone dosage was increased to 75 mg; sulfamethoxazole with trimethoprim was also started. Owing to allergic side effects, the antibiotics were changed to clindamycin and primaquin. Immunosuppressive agents other than prednisolone were considered but found too risky due to the underlying disease.

Dyspnoea improved but after 2 months, the patient reported of an increasing cough. BAL was positive for *H. influenzae* but negative for *P. jirovecii*, mycobacteria, fungi and viral antigens. Oral pivampicillin improved the cough, but once antibiotics were discontinued, the cough returned after 2–3 days in spite of normal CD4 count and IgG.

Prophylactic pivampicillin 350 mg once a day for 3 months was tried but symptoms relapsed again shortly after discontinuation and the cough now progressed; the dosage was increased to 700 mg. Multiple chest X-rays were normal and PFT showed slow but steady improvement of lung function, thus the prednisolone was tapered.

The patient still had recurrent infections and a new BAL again showed lymphocytic inflammation and *H. influenzae*. Ciprofloxacin monotherapy, later in combination with pivampicillin, was prescribed, but symptoms relapsed again after discontinuation.

Chronic sinusitis was found and treated but without effect. Owing to the severe cough compromising sleep and occupation, colistimethate-sodium inhalation (Swedish Orphan Biovitrum) of 1 mio IU (80 mg) pr vial two times per day, administered with a Pari LC nebuliser, was started, resulting in complete remission of all symptoms. No side effects such as bronchospasm or urticaria were observed.

After 1 year, dyspnoea returned with symptoms similar to the former *P. jirovecii* infection. TLCO was decreased to 29% and HRCT showed massive ground glass opacities. Bronchoscopy

Figure 2 Left: High-resolution CT before and 3 months after initial prednisolone treatment. Right: Non-necrotising granulomas (*) and peribronchial inflammation.

found no pathogens and the patient was started on high-dose prednisolone. Owing to clinical suspicion of *P. jirovecii*, tazobactam, clindamycin and primaquine were started, resulting in immediate resolution of symptoms. Owing to allergy, antibiotics were replaced by pentamidin inhalations 300 mg once a day every second week. Pentamidin was later replaced by oral diaminodiphenyl-sulfone 100 mg once a day and prednisolone was tapered. Daily inhalation with colistimethate-sodium was continued.

The patient has now been treated with diaminodiphenyl-sulfone, colistimethate-sodium and human immunoglobulin replacement therapy (later changed to Hizentra 10 000 mg subcutaneous twice a week) for the past 3 years and has had no respiratory infections, and a slow, but steady improvement of PFT has been observed.

DISCUSSION

This case describes the first confirmed case of GL-ILD related to Good's syndrome and it is also the first case with a successful outcome. A possible single previous case speculated that a 53-year-old man with Good's syndrome, where HRCT found pulmonary granulomas, had GL-ILD since the patient had known sarcoidosis.⁴ The patient was treated for a pneumocystis infection but died, presumably due to an uncontrollable candida infection.

Granulomatous lung disease in Good's syndrome has not previously been systematically investigated and is probably underdiagnosed. GL-ILD in patients with CVID was first reported in 1973, but its importance has only recently been acknowledged.^{5–6} However, GL-ILD might also be a complication of Good's syndrome, since patients with both diseases suffer from hypogammaglobulinaemia. Owing to previously limited knowledge of the condition, the significance of GL-ILD in Good's syndrome is unknown, but correct and early recognition could very well be essential for patient survival, as has been described in CVID.⁶ Good's syndrome is rare compared to CVID, but has a highly increased 10-year mortality of 66% compared to 5% in CVID in a single centre follow-up.⁷

The occurrence of autoimmune complications has so far been thought to contribute significantly to the high mortality in Good's syndrome.¹ Similarly, it has been recognised that early diagnosis of GL-ILD in CVID is essential for improved morbidity and survival.^{8–9}

Good's syndrome and interstitial lung disease with ground glass opacities and centrilobular nodules, should lead to further investigations with BAL and biopsies in order to diagnose GL-ILD, and to exclude opportunistic infections.

Recurrent sinopulmonary infections are another well known complication of Good's syndrome and CVID, and only immunoglobulin substitution has shown a significant effect.^{1–3, 8} Some patients have recurrent infections in spite of immunoglobulin administration, and several different prophylactic antibiotic regimes including azitromycin and clarithromycin have been tried with some success.^{3, 10} However, no consensus on prophylaxis exists. Our patient had recurring infections with *H. influenzae* despite immunoglobulin replacement therapy and repeated treatment with pivampicillin, cephalosporin and quinolones, and the patient experienced relapse when treatment was discontinued. He was stabilised on inhaled colistimethate-sodium, and this represents, to our knowledge, the first report of successful colistimethate-sodium prophylaxis of *H. influenzae* in an immunocompromised patient.¹¹ Administration by inhalation theoretically allows for larger doses to the target organ and fewer systemic side effects; inhaled colistimethate-sodium could thus be a new alternative for prophylactic antibiotic treatment in patients with recurrent sinopulmonary infections with encapsulated bacteria.¹²

Opportunistic infections represent another known, although rare, complication.^{1–3} Our patient suffered from one confirmed and one likely infection of *P. jirovecii*, resulting in severe lung function decline. Opportunistic infections, especially with pneumocystis, are often difficult to diagnose, and awareness should be enhanced in difficult-to-treat cases. Sulfamethoxazole and trimethoprim are first-line therapies, but due to allergy, our patient was treated with pentamidin inhalations and, later, with oral diaminodiphenyl-sulfone and has not had any infections for the past 4 years.¹³

Learning points

- ▶ Good's syndrome is a rare but serious primary immunodeficiency with a high mortality rate.
- ▶ Patients with thymoma and hypogammaglobulinaemia should be further investigated for Good's syndrome.
- ▶ Patients with Good's syndrome or other primary immunodeficiencies, who suffer from respiratory distress, should be tested for granulomatous-lymphocytic interstitial lung disease and treated accordingly.
- ▶ Infections with *Pneumocystis jirovecii* are often difficult to diagnose, and attention should be enhanced in difficult-to-treat cases with immunocompromised patients.
- ▶ Inhaled colistimethate-sodium could be a new alternative for prophylactic antibiotic treatment in patients with recurring sinopulmonary infections with encapsulated bacteria.

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REFERENCES

- 1 Kelesidis T, Yang O. Good's syndrome remains a mystery after 55 years: a systematic review of the scientific evidence. *Clin Immunol* 2010;135:347–63.
- 2 Joven MH, Palalay MP, Sonido C. Case report and literature review on Good's syndrome, a form of acquired immunodeficiency associated with thymomas. *Hawaii J Med Public Health* 2013;72:2:56–62.
- 3 Ogoshi T, Ishimoto H, Yatera K, et al. A case of Good syndrome with pulmonary lesions similar to diffuse panbronchiolitis. *Intern Med* 2012;51:1087–91.
- 4 Lee SH, Lee SM, Yang SC, et al. A case of granulomatous lung disease in a patient with Good's syndrome. *Korean J Intern Med* 2008;23:219–22.
- 5 Liebow AA, Carrington CB. Diffuse pulmonary lymphoreticular infiltrations associated with dysproteinemia. *Med Clin North Am* 1973;57:809–43.
- 6 Bates CA, Ellison MC, Lynch DA, et al. Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. *J Allergy Clin Immunol* 2004;114:415–21.
- 7 Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q J Med* 1993;86:31–42.
- 8 Park JH, Levinson AI. Granulomatous-lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin Immunol* 2010;134:97–103.
- 9 Prasse A, Kayser G, Warnatz K. Common variable immunodeficiency-associated granulomatous and interstitial lung disease. *Curr Opin Pulm Med* 2013;19:503–9.
- 10 Kadota J, Mukae H, Ishii H, et al. Long-term efficacy and safety of Clarithromycin treatment in patients with diffuse panbronchiolitis. *Respi Med* 2003;97:844–50.
- 11 Dhariwal AK, Tullu MS. Colistin: re-emergence of the "forgotten" antimicrobial agent. *J Postgrad Med* 2013;59:208–15.
- 12 Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis* 2006;6:589–601.
- 13 Green H, Paul M, Vidal L, et al. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. *Cochrane Database Syst Rev* 2007;(3): CD005590.

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