Unusual association of diseases/symptoms

Good's syndrome and IgA monoclonal gammopathy of undetermined significance

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Summary

Characterised by the association of a thymoma, hypogammaglobulinaemia, and B-cell and T-cell dysfunction, Good's syndrome (GS) is a rare cause of adult immunodeficiency leading to recurrent infections, and autoimmune manifestations related to the thymoma. We describe a 70-year-old woman in whom the diagnosis of GS was made after 7 years follow-up of a monoclonal gammopathy of undetermined significance (MGUS). After thymectomy, she received monthly intravenous immunoglobulin perfusions in order to maintain a normal plasmatic IgG level. To our knowledge, this is the fifth described case of GS associated with an MGUS. This rare condition should not be misdiagnosed, as the prognosis is determined by infectious and autoimmune complications, which could be prevented.

BACKGROUND

Good's syndrome (GS) is a rare cause of adult immunodeficiency, involving both cellular and humoral immunity characteristic features are the association of a thymoma, hypogammaglobulinaemia and B-cell and T-cell defects. Individuals are prone to recurrent bacterial, viral and fungal infections due to immunodeficiency and autoimmune manifestations related to the thymoma.¹

We describe a 70-year-old woman in whom the diagnosis of GS was made after 7-year follow-up of a monoclonal gammopathy of undetermined significance (MGUS). This fourth described the case of GS associated with a monoclonal gammopathy enhance the importance of not misdiagnose a GS in case of an MGUS associated with a hypogammaglobulinaemia. Indeed, the prognosis is determined by infectious and autoimmune complications, which could be prevented.

CASE PRESENTATION

A 70-year-old woman had a medical history of monoclonal gammopathy diagnosed in 2004 during an ophthalmic zoster examination. She was presenting for several years recurrent fungal skin infections, labial herpetic recurrences, chronic diarrhoea and frequent exacerbations of chronic obstructive pulmonary disease. Laboratory findings disclosed an IgA κ monoclonal gammopathy and a restriction in the synthesis of other immunoglobulins (figure 1). Urine examination revealed a κ Bence-Jones proteinuria (0.09 g/24 h). A bone-marrow aspiration showed a plasma cells medullar infiltration rate of 3–5% without any cell line abnormality. Plasmatic calcium and creatinin levels were normal. No bone damage was shown on MRI. The diagnosis of MGUS was proposed and a biannual follow-up organised, showing no evolution of the observed abnormalities. Recurrent diarrhoea and infections persisted without gravity.

In March 2011, she was admitted in hospital for an acute pyelonephritis, labial herpetic recurrence and fungus folds. A new evaluation of the MGUS showed the IgA peak and hypogammaglobulinaemia at known levels. A new bone marrow aspiration, MRI and other laboratory findings failed to disclose any abnormality. HIV serological test was negative as well as an autoimmune assessment. Chest x-ray examination pointed out a left middle mediastinal enlargement, which, a posteriori, already existed on 2004 x-rays (figure 2A). A chest CT scan confirmed a well-limited tumoral mass in the left anterior mediastinum suspicious for thymoma (figure 2B). Pathological examination of the thymectomy revealed a thymoma of AB type, without any sign of malignancy. There were neither clinical nor electromyographic evidence of myasthenia gravis and acetylcholine receptor antibodies were negative. The lymphocyte immunophenotyping showed a total deficit in B cells and an inversion of the CD4/CD8 ratio.

DIFFERENTIAL DIAGNOSIS

The stability of monoclonal peak, the absence of anaemia, hypercalcaemia, renal failure and bone lesions on MRI, as well as the two normal bone marrow aspirations allowed ruling out the diagnosis of myeloma.

The other causes of immunodeficiency appeared to be less likely: (1) HIV serological test was negative; (2) the absence of medullar infiltration by abnormal cells excluded a malignant haemopathy and (3) other humoral immunodeficiencies usually begin earlier, such as common variable immunodeficiency (CVID) or the X linked agammaglobulinaemia.

Pathological examination of the thymus confirmed the diagnosis of benign thymoma. There was no evidence for another malignant condition.

Figure 1 Comparison of plasmatic protein electrophoresis (A), plasmatic immunoglobulin level and lymphocyte count (B) before and after thymectomy.

Finally, the absence of electromyographic abnormalities, the negativity of acetylcholine receptor antibodies and autoimmune serologies excluded an associated myasthenia gravis or other autoimmune diseases.

OUTCOME AND FOLLOW-UP

One year after thymectomy, the patient was still presenting benign infections and required monthly intravenous immunoglobulin (IVIG) perfusions to keep IgG plasmatic

Figure 2 Chest x-ray (A) disclosing a left middle mediastinal enlargement (arrow), confirmed by CT scan (B) showing a tumoral mass in the left anterior mediastinum (arrow).

level up to 6 g/l. Deficit in other immunoglobulins, IgA peak and lymphocyte immunophenotyping remained stable.

DISCUSSION

Described for the first time in 1954, GS associates a thymoma with and acquired humoral and cellular immunodeficiency including hypogammaglobulinaemia, low or absent B lymphocytes and variable defects in cell-mediated immunity (low CD4 lymphocytes, inverted CD4/CD8 T-cell ratio and reduced T-cell mitogen proliferative response).¹

Men and women are equally affected, usually in their fourth or fifth decade. The exact prevalence of GS is unknown but it represents 1–2% of patients with primary immunodeficiency receiving IVIG replacement.²

The immunodeficiency pathogenesis in GS remains unclear but may proceed from a secretion of interferon-like cytokines by bone marrow stromal cells, leading to an alteration of growth and differentiation of B-cells and thymocyte precursors.^{2–3} The link between humoral and cellular immunodeficiency is also poorly understood. Thymoma could cause immunodeficiency because of its implication in physiological immunosurveillance, especially in T-lymphocyte maturation. Moreover, the immunoglobulin production by B cells may be inhibited by autoantibodies or activated T cells.² In contrast, it is also envisaged that the compensatory mechanism of immunodeficiency leads to a hyperplastic change of the thymus resulting in a thymoma.⁴ Some studies investigated the role of some genetic factors, such as various subtypes of HLA, or mutation of tumour necrosis α receptor superfamily (TNFRSF13B) found in one patient with GS, and also implicated in CVID.⁵ TNFRSF13B gene encodes the TACI protein, a part of the tumour necrosis factor receptor which dysfunction leads to a defective B-cell proliferation and differentiation.

Main pathological finding is benign thymoma (>90%) of AB type (ie, spindle cell variant, >50%) which is frequently associated with parathymic syndromes.⁶ Half of all patients with thymoma are asymptomatic. Others may complain of compressive symptoms. Approximately 60% of patients suffer from parathymic syndromes, which are either paraneoplastic or autoimmune. Autoimmune manifestations are frequent such as pure red cell aplasia, myasthenia gravis and oral lichen planus (35%, 15% and 12% of cases, respectively).⁶ Other rarer autoimmune conditions are possible. Despite depressed immunoglobulin synthesis, autoimmune antibodies are found in 30–50% of cases and the most common are antinuclear antibodies (55%) followed by anti-striated (30%) and antithymic antibodies (20%).⁶

Infectious complications mostly concern respiratory tracts, mainly caused by *Haemophilus influenzae* and *Pseudomonas* spp., and more rarely by viral (mostly cytomegalovirus (CMV)) or fungal (*Candida* spp., *Aspergillus* spp. and *Pneumocystis jirovecii*) agents.⁷ Recurrent respiratory infections can lead to bronchiectasis. Chronic diarrhoea is present in 50% of patients and may be related to an infection with enteric bacteria, *Giardia lamblia* or CMV. Frequently, no infectious agent is found. In contrast with other humoral primary immunodeficiencies, patients with GS may develop opportunistic infections, which suggest severe defects in cellular immunity. The most frequent are mucocutaneous candidiasis, herpes zoster and recurrent herpes simplex virus infections. Hypogammaglobulinaemia is considered as a

characteristic feature of GS, although some patients with a thymoma and a clear clinical picture of immunodeficiency have been described with a normal immunoglobulin plasmatic level.⁸ The level of gammaglobulins seems to be a good predictor of immunity. Panhypogammaglobulinaemia is found in 75% of cases but a deficit in two or only one γ -globulin class may also be found. To date, only four other GS with monoclonal production of immunoglobulins had been reported.^{9–12} The origin and pathophysiological significance of this monoclonal gammaglobin peak is unknown but may be interpreted as a parathymic syndrome, or an associated MGUS, which occurs in 3% of general population older than 50 years.¹³ Few or absent B cells (87% of patients) may explain the lack in γ -globulin synthesis. Because of the severity of infections, associated autoimmune diseases and the depth of the immunodeficiency, the prognosis of GS is worse than other primary immunodeficiencies. When 100% and 95% of patients with a CVID are still alive at 5 and 10 years, respectively, remaining alive patients with a GS are 70% and 33%. Infections are the cause of death in about 60% of cases.⁶

The complete thymoma resection is considered as the most important long-term prognostic factor to avoid local invasion and metastatic spread. If thymectomy has a favourable effect on autoimmune manifestations, it is ineffective on immunodeficiency state. IVIG supplementations improve infection control with a reduction of hospitalisation, a decreased use of antibiotics, and a possible prevention of the risk of chronic lung damage and bronchiectasis.⁷ IVIG are usually monthly administered to keep the plasmatic IgG level up to 6 g/l.

In conclusion, GS should be considered in adults with unexplained immunodeficiency. The most typical form associates a thymoma with both cellular and humoral immunity deficiency, characterised by hypogammaglobulinaemia and lymphopaenia. A monoclonal hypergammaglobulinaemia is exceptional but should not lead to eliminate the diagnosis. As well, in the assessment of monoclonal gammopathy associated with hypogammaglobulinaemia and recurrent infections, after eliminating myeloma, we advise one to realise a lymphocyte immunophenotyping and CT scan to disclose a thymoma in order not to misdiagnose a GS. Indeed, this particular primary immunodeficiency requires a specific management in order to reduce morbimortality, such as thymoma removal, IVIG replacement, specific treatment of infections and sometimes immunosuppressive therapies.

Learning points

- ▶ Good's syndrome (GS) should be considered in adults with unexplained immunodeficiency.
- ▶ The most typical form of GS associates a thymoma with both cellular and humoral immunity deficiency. Clinical manifestations include compressive complications due to thymoma, recurrent infections and autoimmune manifestations.
- ▶ The assessment of monoclonal gammopathy with hypogammaglobulinaemia leading to recurrent infections should include a lymphocyte immunophenotyping and a CT scan to disclose a thymoma, in order not to misdiagnose a GS.

Competing interests None.

Patient consent Obtained.

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