Clin Exp Med (2008) 8:171–173
DOI 10.1007/s10238-008-0175-x

SHORT COMMUNICATION

Myelodysplasia and Good syndrome. A case report

M. Di Renzo · A.L. Pasqui · L. Voltolini · G. Gotti · G. Pompella · A. Auteri

Received: 12 January 2008 / Accepted: 13 March 2008

Abstract Good syndrome (GS) is a rare adult-onset immunodeficiency disease characterised by hypogammaglobulinaemia and thymoma. Here we describe a 72-year-old male patient who was diagnosed with GS when he was 62, after a two-year history of recurrent respiratory infections. A chest CT scan showed a mediastinal mass which was surgically removed; its histology revealed a thymoma. The patient was hypogammaglobulinaemic and his clinical condition dramatically improved after starting an appropriate dosage of IVIG. Two years ago he developed a normochromic normocytic anaemia requiring several transfusions. A bone marrow biopsy revealed a myelodysplastic syndrome. The patient started cyclosporine and the anaemia gradually improved, achieving transfusion independence.

Keywords Good syndrome · Myelodysplasia · Cyclosporine

M. Di Renzo (✉)
U.O. di Medicina III, Policlinico Le Scotte,
Viale Bracci 16, 53100 Siena, Italy
e-mail: cd28apo@hotmail.com

A.L. Pasqui · G. Pompella · A. Auteri
Department of Internal Medicine and Immunological Sciences,
Section of Internal Medicine,
University of Siena,
Siena, Italy

L. Voltolini · G. Gotti
Department of Thoracic Surgery,
Section of Thoracic Surgery,
University of Siena,
Siena, Italy

Introduction

Good syndrome (GS) was first described in 1954 by Good and colleagues, who first reported hypogammaglobulinaemia in a small percentage of patients with thymoma [1]. GS is an adult-onset immunodeficiency characterised by hypogammaglobulinaemia, low or absent B cells in the peripheral blood and, variably, defects in cell-mediated immunity. GS was often considered as a subset of common variable immunodeficiency (CVID) with thymoma, whereas nowadays it is regarded as a distinct clinical entity whose pathogenesis is still uncertain [2]. A bone marrow defect impairing B-cell maturation has been suggested and deficiencies in other cell lineages with eosinopenia, pure red cell aplasia or neutropenia are often reported.

Here we report a case of a male patient affected by GS and previously described [3] who developed a myelodysplastic syndrome that was successfully treated with cyclosporine.

Case report

A 72-year-old male patient was diagnosed with Good syndrome ten years ago after recurrent respiratory infections: he had had recurrent otitis, recurrent bronchitis, pneumonia and sinusitis. Blood tests had revealed hypogammaglobulinaemia and mild neutropenia (1200/mm^3) and he had undergone a bone marrow aspirate which had not shown any abnormality. A chest X-ray showed a mediastinal mass confirmed by a chest CT-scan with agobiopsy which revealed lymphoid cells. The mass was resected, showing a mixed epithelial and lymphocytic thymoma with infiltration of the capsula. The total number of lymphocytes was normal, but the CD4+

T-cell count was 420/ml, with an inverted CD4/CD8 ratio of 0.39 and absent peripheral B cells. PPD skin reactivity was positive. *In vitro* lymphocyte proliferation was normal. Due to its low serum levels of IgG (24 mg/dl, normal >700), IgM (5 mg/dl, normal >40) and IgA (5 md/dl, normal >70), monthly IVIG infusions were started and the patient had a gradual improvement in his conditions.

In January 2005 the patient started complaining of asthenia after undergoing an operation of anal fistula two months before. The laboratory findings showed a red blood cell count of 2.42×10^{12}/l, haemoglobin of 8.1 g/dl, haematocrit of 23.6% and mean corpuscular volume 97.2 fl. He underwent treatment with erythropoietin, vitamin B12 and folate, but after three months, due to the persistence of the anaemia, he underwent a myelobiopsy which revealed a myelodysplastic syndrome with characteristics of refractory anaemia. In May 2005 his haemoglobin levels started improving (haemoglobin of 9.9 g/dl), however they remained the same as before after three weeks. In September 2005 he started cyclosporin A at a dosage of 50 mg twice a day. Haemoglobin levels increased progressively, reaching 10.9 g/dl after one and a half months of treatment and 12.5 g/dl after three months, allowing transfusion independence. The patient has not developed hypertension, renal failure or opportunistic infection in spite of the immunosuppressive treatment, even though he has been taking itraconazole since 1997, when he was affected by Candida esophagitis. The total number of CD4+ is still reduced, with an inverted CD4/CD8 ratio of 0.38 and absent peripheral B cells. *In vitro* lymphocyte proliferation is still normal.

Discussion

Immunodeficiency associated with thymoma was described nearly fifty years ago and was classified as one of the first immunodeficiency diseases [1]. Patients with GS are usually middle-aged or elderly when, after being well all their life, they begin to be highly susceptible to infections [4]. It is usually the infections rather than the local symptoms due to the mediastinal mass that call attention to the thymic enlargement. Our patient was diagnosed with GS after recurrent respiratory infections thanks to a chest X-ray which showed a mediastinal mass. Actually only 3–6% of patients with thymoma are hypogammaglobulinaemic and the relationship between thymoma and the immune dysfunction is not clear: thymoma does not seem to induce hypogammaglobulinaemia because after it is surgically removed because of its potentially invasive growth and metastatic spread (in our patient the tumour had already invaded the capsula) the immune impairment persists. Our patient, after thymectomy, continued to show a reduction of all the three main antibody classes, with almost undetectable levels of IgA and IgM and very low IgG.

The deficient humoral immunity in GS is the main cause of the recurrent respiratory infections, which are mainly sustained by encapsulated bacteria with an overall spectrum of manifestations and pathogens similar to other hypogammaglobulinaemic conditions, such as CVID. However, in GS, opportunistic infections, such as mucocutaneous candidiasis, herpes zoster, *P. carinii* pneumonia and recurrent HVS infections develop more frequently than in CVID and seem to be due to defects in cell-mediated immunity: several patients with GS show skin anergy, lymphocytopenia, CD4+ lymphocytopenia and a depression of *in vitro* lymphocytic response [4]. In our patient, CD4+ T cells were reduced with an inverted CD4/CD8 ratio, as is often reported in GS [4].

Several haematological disorders have been reported in GS, including pure red cell aplasia, pancytopenia and autoimmune haemolytic anaemia [2]. The target in many of these disorders appears to be the stem cell committed to a haematopoietic lineage with loss of that lineage, even if the role of autoantibody-mediated mechanisms in the destruction of the lineage cannot be excluded. Our patient developed anaemia 8 years after being diagnosed with Good syndrome: myelobiopsy revealed a refractory anaemia which is a classified as a myelodysplastic syndrome.

Myelodysplastic syndromes are a set of oligoclonal disorders of haematopoietic stem cells in which ineffective haematopoiesis manifests clinically as anaemia, neutropenia and/or thrombocytopenia of variable severity [5]. Some myelodysplastic syndromes may progress to acute myelogenous leukaemia but the risk is low as regards refractory anaemia [5], which affected our patient and to our knowledge has never been described before in Good syndrome. The aetiology of myelodysplastic syndromes is unknown. Supportive care consists of transfusions to correct anaemia and this was the first approach in our patient. However, more recently, new treatments such as immunosuppressive agents such as anti-thymocyte globulin and cyclosporine have been proposed, because T-cell-mediated immune suppression of haemopoiesis has been suggested [6].

In myelodysplastic syndrome immune dysfunction has been described: abnormal CD4/CD8 ratio and increased activated cytotoxic T cells with a higher percentage of CD8+CD28– cells have been described as well as skewing of the T-cell receptor Vb complimentarity-determining region 3 pattern consistent with T-cell oligoclonal expansion [7, 8]. These data support the use of immunosuppressive agents in this syndrome.

Cyclosporine is a potent immunosuppressive agent that operates by blocking synthesis and/or release of IL2 from helper T cells, thereby inhibiting the expansion of unprimed helper T cells, cytotoxic lymphocytes and T-cell-dependent B-cell activation. Cyclosporine also sup-

presses other cytokines, such as TNF-α, interferons and transforming growth factor-β, which are capable of inhibiting haemopoiesis [9]. Cyclosporine is effective in 60% of myelodysplastic patients and especially in those affected by refractory anaemia, inducing a rise in haemoglobin levels and sometimes transfusion independence [6]. Our patient achieved transfusion independence after two months of treatment in agreement with the average time of response to therapy reported by other authors [6]. Moreover the patient did not develop opportunistic infections, probably due to the low dosage of the drug and in agreement with the fact that the risk of secondary infection with cyclosporine is lower than with other immunosuppressive drugs; actually the lymphocyte proliferation of our patient after starting cyclosporine is still within the normal range.

It is important to underline the fact that in Good syndrome a clonal expansion of CD8+BV8 T lymphocytes has been described and it has been suggested that these cells play a role in the pathogenesis of the disease, inducing B-cell loss [10]. It is likely that in our patient the same clone suppresses haematopoiesis and the treatment with cyclosporine is effective because it inhibits this clone.

Conflict of interest statement The authors declare that they have no conflict of interest related to the publication of this manuscript.

References

1. Good RA (1954) Agammaglobulinemia – a provocative experiment of nature. Bull Univ Minn 26:1–19
2. Cunningham-Rundles C, Agarwal S (2007) Thymoma and immunodeficiency (Good syndrome): a report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol 98:185–190
3. Di Renzo M, Pasqui AL, Bruni F et al (2004) Thymoma and immunodeficiency. N Z Med J 117:U750
4. Tarr PE, Sneller MC, Mechanic LJ et al (2001) Infections in patients with immunodeficiency with thymoma (Good syndrome). Medicine 80:123–133
5. Catenacci DVT, Schiller GJ (2005) Myelodysplastic syndromes: a comprehensive review. Blood Rev 19:301–319
6. Dixit A, Chatterjee T, Mishra P et al (2005) Cyclosporin A in myelodysplastic syndrome: a preliminary report. Ann Hematol 84:565–568
7. Melenhorst JJ, Eniafe R, Follmann D et al (2002) Molecular and flow cytometry characterization of the CD4 and CD8 T-cell repertoire in patients with myelodysplastic syndrome. Br J Haematol 119:97–105
8. Epperson DE, Nakamura R, Sauntharajah Y et al (2001) Oligoclonal T cell expansion in myelodysplastic syndrome: evidence for an autoimmune process. Leuk Res 25:1075–1083
9. Ferraccioli GF, Tomietto P, De Santis M (2005) Rationale for T-cell inhibition by cyclosporine A in major autoimmune diseases. Ann N Y Acad Sci 1051:658–665
10. Masci AM, Palmieri G, Vitiello L et al (2003) Clonal expansion of CD8+BV8T lymphocytes in bone marrow characterizes thymoma-associated B lymphopenia. Blood 101:3106–3108