Complete remission of pure white cell aplasia associated with thymoma, autoimmune thyroiditis and type 1 diabetes

FUMEAUX, Zina, et al.

Abstract

Pure white cell aplasia (PWCA) is a rare disorder of unknown origin, often associated with thymoma, characterized by selective neutropenia or pure agranulocytosis, and absence of granulocyte precursors in the bone marrow, but with normal erythroblasts and megakaryocytes. We report a case of PWCA associated with thymoma. Unusual findings in this case report included simultaneous presence of autoimmune thyroiditis, type 1 diabetes, anti-striated muscle antibodies, and the presence in the peripheral blood of CD8+ T cells that expressed a homogeneous naive phenotype. Neutrophil count became normal on immunosuppressive therapy after thymectomy.

Reference


DOI : 10.1034/j.1600-0609.2003.00023.x
PMID : 12605664

Available at:
http://archive-ouverte.unige.ch/unige:44719

Disclaimer: layout of this document may differ from the published version.
Case Report

Complete remission of pure white cell aplasia associated with thymoma, autoimmune thyroiditis and type 1 diabetes


Abstract: Pure white cell aplasia (PWCA) is a rare disorder of unknown origin, often associated with thymoma, characterized by selective neutropenia or pure agranulocytosis, and absence of granulocyte precursors in the bone marrow, but with normal erythroblasts and megakaryocytes. We report a case of PWCA associated with thymoma. Unusual findings in this case report included simultaneous presence of autoimmune thyroiditis, type 1 diabetes, anti-striated muscle antibodies, and the presence in the peripheral blood of CD8+ T cells that expressed a homogeneous naive phenotype. Neutrophil count became normal on immunosuppressive therapy after thymectomy.

Pure white cell aplasia (PWCA) is defined as agranulocytosis with absence of myeloid precursors in the bone marrow. Erythropoiesis and thrombopoiesis are preserved. PWCA was first described in association with an inhibitory activity of immunoglobulins (Ig) G and M on granulopoiesis (1). Association with thymoma was reported later (2), as well as evidence of an inhibitory effect of circulating IgG on granulocyte-monocyte forming units (2, 3). There are only four descriptions of primary PWCA (3–6). Secondary PWCA has been described with ibuprofen (7) and chlorpropamide (8), with complement activation by a specific antibody exclusively in the presence of the drug. We report a case of PWCA associated with thymoma and unusual findings including simultaneous presence of autoimmune thyroiditis, type 1 diabetes, and anti-striated muscle antibodies. Immunophenotype studies of peripheral blood lymphocytes revealed the presence of an 'atypically' homogeneous CD8+ T-cell population with a naive phenotype.

Case report

One year prior to presentation, a 76-yr-old woman was diagnosed with autoimmune diabetes (islet cell antibodies 20 000 U JDS, n.v. < 10) and thyroiditis (thyreoperoxidase 391 IU/mL, n.v. < 100 and thyreoglobulin antibodies 1977 IU/mL, n.v. < 200) with hypothyroidism. Adrenal insufficiency was ruled out and adrenal antibodies were negative. She was admitted for asthenia, fever, weight loss, diarrhoea, odynophagia and hyperglycaemia, while on treatment with insulin and thyroid hormones. As pain reliever she was taking mefenamic acid, which was stopped on admission. Blood pressure was 100/60 mmHg, pulse rate 110/min, and temperature 38.2°C. The abdomen was diffusely painful, without hepatosplenomegaly. Hematocrit was 25.2%, white cell count 2.8 G/L (neutrophils 0%, lymphocytes 95%, eosinophils 0%, basophils 1%, monocytes 2%, and plasmocytes 2%), and platelet count 238 G/L. C-reactive protein was 161 mg/L, sodium 123 mmol/L, potassium 2.9 mmol/L, and...
glucose 20.9 mmol/L. Renal and liver functions were normal. Antinuclear antibodies were negative, but anti-striated muscle antibodies were positive (1/320, n.v. < 1/20). Broad-spectrum antibiotic therapy was instituted. The differential diagnosis for isolated neutropenia included bone marrow disorder (lymphoproliferative syndrome), drug-induced (mefenamic acid), post-infection (Epstein–Barr virus, cytomegalovirus, human immunodeficiency virus, herpes simplex virus), or autoimmune disorder. Peripheral lymphocyte typing showed no monoclonal B lymphocytes. A bone marrow biopsy showed the absence of myeloid precursors and the presence of large numbers of lymphocytes, mainly CD8+ T cells. The diagnosis of PWCA was retained.

Magnetic resonance imaging revealed a solid mass in the left paracardial region (Fig. 1A). The patient underwent thymectomy, and histology confirmed a malignant cortical thymoma, type B2 (Figs 1B, C, and D). High dose intravenous immunoglobulins (IVIg) and granulocyte-colony stimulating factor (G-CSF), ineffective before thymectomy, induced a sustained rise in neutrophils when given in association with 3-d pulsed methylprednisolone after thymectomy (Fig. 2). One month later, the patient was readmitted for relapsing agranulocytosis without relevant findings on physical examination. High doses of IVIg (15 g/d) were ineffective; however, agranulocytosis resolved 3 d later with G-CSF, cyclosporin A (CsA; 3 mg/kg/d in two doses) and prednisone, 1 mg/kg/d (Fig. 2). It is worth mentioning that CsA was administered at the standard immunosuppressive dose and eventual toxicity of the drug was monitored by measuring the creatinine level. Follow-up after 24 months showed sustained remission. Prednisone was given in diminishing doses for 1 yr and then stopped. CsA was given for 20 months at the doses shown in Fig. 2.

Materials and methods

Peripheral blood mononuclear cells were purified using Ficoll-Paque (Pharmacia, Uppsala, Sweden) gradient centrifugation. Staining was performed using monoclonal antibodies directed against CD3, CD4, CD8, CD45RA, CD27, or isotype matched irrelevant antibodies, directly coupled to FITC, PE or Red 670 in order to perform three colour analysis. Events were acquired by flow cytometry and analysed using the CellQuest software (FACScalibur, Becton-Dickinson, Sunnyvalley, CA, USA).

Results and discussion

Diagnosis of PWCA was confirmed in our patient by a bone marrow examination. Thymic investigation was performed because PWCA is frequently associated with thymoma, in some cases even many years after removal of the tumour (9), and because the anti-striated muscle antibodies were positive.

The PWCA has an autoimmune pathogenesis with, in the majority of cases, an antibody-mediated specific toxicity on the myelomonocytic precursor cells, which distinguishes it from other immune peripheral neutropenias. Thymoma is
frequently associated with autoimmune manifestations. However, absence of myelopoiesis, as in our case, has been described in only four cases (10–13). Bone marrow showed a promyelocyte arrest in five other cases (2, 9, 13–15).

Although several autoantibodies are characteristic of agranulocytosis associated with thymoma (9, 12, 13, 15), the simultaneous presence of antibodies to the striated muscle, islet cells, thyreoglobulin and thyroid thyreoperoxidase, such as in our case, has not previously been reported.

As in our case agranulocytosis recurred 30 d after thymectomy, it can be argued that thymoma by itself was not directly responsible for PWCA. Although several autoantibodies are characteristic of agranulocytosis associated with thymoma (9, 12, 13, 15), the simultaneous presence of antibodies to the striated muscle, islet cells, thyreoglobulin and thyroid thyreoperoxidase, such as in our case, has not previously been reported.

As in our case agranulocytosis recurred 30 d after thymectomy, it can be argued that thymoma by itself was not directly responsible for PWCA. This is consistent with other reports showing that thymectomy does not cure the autoimmune manifestations accompanying thymomas (16). However, it has been recently demonstrated that thymomas associated with myasthenia gravis are also associated with increased numbers of mature circulating T cells expressing a naive phenotype. This has been assessed by studying the surface expression of CD45RA on T cells, particularly CD8+ T cells, as well as the numbers of T cells containing episomal T-cell excision circles which directly reflect thymic output (17, 18). We therefore analysed the phenotypes of the peripheral blood T cells that represented 82% of the mononuclear cells 2 d before thymectomy. Forty-six per cent of the CD3+ cells were CD4+ whereas 52% were CD8+. Interestingly, virtually all (98.4%) of the CD3+CD8+ cells co-expressed CD45RA and CD27, which makes them indistinguishable from true naive T cells (19). CD8+CD45RA+CD27+ T cells represent the majority of CD8+ T cells in cord or newborn blood, whereas their number decreases with age along with antigen encounter and immunological experience. Thus, after the age of 50 yr, they represent less than 50% of total CD8+ T cells, the others being memory CD45RA–CD27+ and effector CD45RA+CD27– cells. The CD4+ T-cell subset distribution in our patient was less skewed but still abnormal with 67% CD45RA+CD27+, 21.9% CD45–CD27−, 8.1% CD45+CD27−, and 3% CD45–CD27+ cells (data not shown). Phenotypic analysis performed 2 and 4 months after thymectomy did not show substantial changes in CD8 and CD4 subset distribution. These data indicate a major alteration in the composition of T cells present in the peripheral blood of our patient. Thus, it can be speculated that pre-T cells may repopulate a neoplastic epithelial thymus where they mature in the thymic microenvironment. However, the normal mechanisms leading to positive and negative T-cell selection are somehow altered in thymomas and autoreactive T cell clones are allowed to mature and leave the thymus. These mature autoreactive T cells may

**Fig. 2.** Evolution of granulocyte and leukocyte counts as a function of various therapeutic interventions. I: Intravenous immunoglobulins (1: 2 g/d for 5 d, then 25 g/d for 4 d; 2: 35 g/d for 5 d; 3: 15 g/d for 3 d; 4: 35 g for 1 d). G: Granulocyte colony stimulating factor (1: 30 mio U/d; 2: 30 mio U/d for 7 d, 48 mio U/d for 4 d, 30 mio U/d for 2 d). S: Steroids (1: methylprednisolone 125 mg/d for 1 d, 125 mg t.i.d. for 1 d, 125 mg b.i.d. for 1 d; 2: prednisone 7.5 mg/d for 7 d, 60 mg/d for 3 d, 40 mg/d for 1 d, 30 mg/d for 1 d, then 20 mg/d; 3: prednisone 15 mg/d, with gradual reduction over 4 months to 5 mg/d). C: Cyclosporin A (1: 3 mg/kg b.i.d.; 2: 1.5 mg/kg/b.i.d.).
then encounter, under appropriate conditions, the relevant autoantigen(s), become effector cells, and provide help to B cells for generating autoantibodies. The large spectrum of autoreactivity is particularly well illustrated in our case in which the documented targets of autoantibodies included Langerhans islet beta cells, thyroglobulin and thyroperoxidase of thyroid origin, and the major striational autoantigens.

CsA has been successfully used in several autoimmune haematological cytopenias, including pure red cell aplasia and PWCA with promyelocyte arrest (20–23). Low doses of CsA together with low doses of glucocorticoids proved to be sufficient in our case to maintain long-term remission after thymectomy. Thus, an immunosuppressive therapeutic approach of limited toxicity may be efficacious in controlling the effector function of T cells that mature in an altered thymic environment.

References