

# Diagnostic Dilemma: Lymphocytopenia in a Patient with Thymoma – Side Effect due to Irradiation Treatment or Development of Good's Syndrome?

Klas Raaschou-Jensen<sup>a</sup> Terese L. Katzenstein<sup>b</sup>  
Hanne Marquart<sup>d</sup> Lars Ryder<sup>d</sup> Gedske Daugaard<sup>c</sup>

Departments of <sup>a</sup>Hematology L4042, <sup>b</sup>Infectious Medicine M5131, and <sup>c</sup>Oncology ONK5073, and <sup>d</sup>Tissuetyping Laboratory KI7631, National University Hospital, Rigshospitalet, Copenhagen, Denmark

## Key Words

Thymoma · Thymic tumours · Lymphocytopenia · Good's syndrome · Hypogammaglobulinaemia · Irradiation therapy · Radiation

## Abstract

A case of persistent B-cell lymphocytopenia in a 40-year-old woman with lymphoid-epithelial thymoma treated with chemotherapy, surgery and irradiation is described. The possible diagnosis of Good's syndrome (hypogammaglobulinaemia and thymoma) is discussed.

Thymomas represent a rare neoplasm of the mediastinum. The incidence is 0.15 cases per 100,000 in the industrialised part of the world [1]. The WHO classifies this neoplasm as an indolent tumour of epithelial tissue, which can be subdivided according to the degree of infiltration of lymphocytes as well as cellular atypia.

Thymomas often relapse locally, and metastatic disease is uncommon. Thymic tumours are usually seen at the age of 40–60 years. They are incidentally identified on an X-ray of the thorax in 50% of the cases; however, only 60–80% of all tumours can be seen on X-ray. MRI or a CT scanning may diagnose the remaining cases. 90% of thymomas are placed in the anterior mediastinum, and 50% of the neoplasms in this region are thymomas [1].

Cough, pain or signs of proximal airway obstruction may be the initial symptoms. In 30% of the cases, the patient is asymptomatic at diagnosis. Diseases such as myasthenia gravis, lupus erythematosus, rheumatoid arthritis, thyroiditis and Sjögren's syndrome, dermatomyositis, primary sclerosing cholangitis, multiple sclerosis and pernicious anaemia can be seen in combination with thymomas [2]. Interestingly, a recent review has found autoimmune manifestations in 58.6% (89 of 152) of patients with Good's syndrome. In particular, pure red cell aplasia was seen in 31 of these 152 cases [3]. Good's syndrome is the combination of thymoma and hypogammaglobulinaemia. Robert Good and colleagues first reported this syndrome in 1954 [4]. Hypogammaglobulinaemia emerges in 6–11% of thymoma patients [5]. The immunological findings in Good's syndrome are mainly hypogammaglobulinaemia with absent or reduced numbers of B lymphocytes, CD4 T lymphocytopenia as well as an inverted CD4/CD8 ratio. The pathogenesis of the syndrome remains elusive [3].

Radiotherapy is a treatment option in patients with localised thymoma. Lymphocytopenia can be observed as a side effect of radiation treatment [2, 6].

We describe a patient with persistent B-cell lymphocytopenia following irradiation treatment and review the possible differential diagnosis of Good's syndrome and thymoma.

### Case Report

A 40-year-old woman was diagnosed in 2004 with a large type B1 (WHO classification) combined lymphoid-epithelial thymoma in the right lung involving the mediastinum. At diagnosis, the tumour measured 12 × 18 × 20 cm, with compression of vena brachiocephalica and vena cava superior, explaining the patient's 1-year suffering from facial and neck oedema. Overall, the patients performance status was excellent.

The patient had stage III disease according to Masaoka staging, with an estimated 5- and 20-year survival rate of 89 and 49%, respectively [7, 8]. Tumour resection was not possible due to the size and the localisation. Chemotherapy with 6 cycles of vincristin, cisplatin, CCNU and prednisolone was initiated and well tolerated. A new CT scan following the 6 chemotherapy cycles showed stable disease.

At that time, the patient still had an excellent performance status with only mild dyspnoea. The patient was referred for surgery in order to reduce the disease burden. Tumour reduction was impossible due to tumour involvement in 2/3 of the right hemi-thorax and affection of the main cervical veins and vena cava superior on the right side. Shortly after the operation, the patient had a normal leucocyte count with normal lymphocytes (table 1). During the following two months, she became more dyspnoeic.

Radiotherapy with 54 Gy was initiated in October 2005 and was well tolerated. This resulted in a clear reduction of the tumour size. The patient still suffered from mild dyspnoea which responded to steroid treatment. In December 2005, the patient exhibited a reactivation of a herpes simplex virus infection on the upper lip and the right cheek. A few days later, she developed fever and mild dyspnoea. Prior to admittance to the hospital, she was treated for 10 days with oral antibiotics without influence on fever and the level of dyspnoea. At hospital admission, the C-reactive protein level was 56 mg/l, and lymphocytopenia of  $0.29 \times 10^9/l$  was measured in a normal leucocyte count. Furthermore, a mild hypogammaglobulinaemia was noted, with an IgM concentration of 0.34 g/l (table 1). IgG and IgA concentrations were normal. Intravenous treatments with ceftriaxon and acyclovir were initiated due to pneumonia and herpes simplex infection. The fever, dyspnoea and raised C-reactive protein level were unchanged at day 4. Immunodeficiency examination the following day raised the suspicion of a Good's syndrome, with almost undetectable amounts of B cells (0.4% of the lymphocytes) and a low CD4 T-cell count of  $0.04 \times 10^9/l$  (table 1). Irradiation-induced pneumonitis could not be excluded, and the patient recovered with a combination of antibiotics and prednisolone treatment. No signs of myasthenia gravis were found. Furthermore, there were no signs of other autoimmune diseases. A year without any upper respiratory or opportunistic infections followed. The patient still had a low lymphocyte count at 18 months, with very low B- and T-cell counts (table 1). HIV test was negative. Three years after irradiation

therapy, the patient had more and long-lasting upper respiratory tract infections. The thymoma was still in a partial remission, and a new immune status 49 months following the irradiation treatment showed a normal lymphocyte count of  $1.8 \times 10^9/l$  (table 1). The T-cell count and the CD4/CD8 ratio has normalised at 1.6. The fraction of virgin CD4+ T cells were markedly raised during this period, indicating increasing thymus function. Meanwhile, the B-cell count remained extremely low. The levels of immunoglobulins including IgM were normal. However, the patient still had recurrent upper airway infections. Initially, in 2006, a normal level of somatic hypermutation (measured on expressed immunoglobulin kappa light chain gene transcripts) was present, indicating that the low but detectable amounts of B cells were normally functioning. Repeated somatic hypermutation assay showed qualitative reduced levels of somatic hypermutation and thereby presumably of affinity maturation of antibodies. This may be the resulting defect of the irradiation therapy causing insufficient CD4 T cell help to the B cells. At present, the patient is in a good performance status and is working part time.

## Discussion

The current treatment of thymoma is primarily resection followed by radiation therapy in case of local disease [2]. Chemotherapy is given to patients with disseminated disease.

In the present case, lymphocytopenia was diagnosed following irradiation treatment. A raised lymphocyte turnover can be seen following radiation therapy or chemotherapy [5, 6]. Especially irradiation is well known to give a mild B-cell and a long-lasting naive T-cell lymphocytopenia, with recovery of lymphocyte counts after 1–6 years [10].

The radiation dose of 54 Gy used in the present case is sufficient for inducing the observed long-lasting lymphocytopenia [6].

Another explanation might be that the patient suffered from Good's syndrome. This is supported by the fact that the B-cell count remained extremely low even though the T cells were restored. Normally, the B-cell count would reconstitute within 1–2 years after radiotherapy [6]. The immunodeficiency in patients with Good's syndrome is acquired and clinically resembles HIV infection. The pathogenesis remains unknown. One main hypothesis is a differentiation deficiency of pre B-lymphocytes. Probably, subtypes of T lymphocytes work as regulators in this differentiation. It has been shown that T lymphocytes from patients with thymomas can inhibit B-lymphocyte production of immunoglobulin in healthy controls [4]. Involvement of the cell-mediated immunity is obvious as opportunistic infections are seen in this disease. It probably has its origin from a CD4+ T-cell lymphocytopenia as well as from a reduced proliferation of T lymphocytes [4]. The cellular deficiency is special in this syndrome. Cryptococcus meningitis or toxoplasmosis has not been seen. In contrast, patients with Good's syndrome seem to develop cytomegalovirus infection at a higher CD4 cell count than for example HIV patients [4].

Other explanations for lymphocytopenia could be renal insufficiency, lymphocyte trapping during viral infection, splenomegaly, septic shock disease, burn, systemic granulomatosis, undernourishment with shortage of zinc and treatment with steroids. It can also be necessary to exclude immunodeficiency diseases such as common variable deficiency, HIV infection, idiopathic CD4+ T lymphocytopenia as well as malignant haematological diseases [5].

In general, thymoma patients should have an immunodeficiency evaluation in case of recurrent infections [11].

The prognosis of patients with Good's syndrome is related to the frequency of infections, changes in the haematological parameters as well as comorbidities such as autoimmune disease.

Good's syndrome patients should be treated with thymectomy, which improves the prognosis but does not change the immune status [11]. Intravenous substitution with immunoglobulin every third week is recommended for patients with frequent infections. The treatment reduces the numbers of infections and hospital stays as well as the use of antibiotics. Furthermore, the treatment prevents the chronic damage of the lung with the risk of bronchiectasis. Prompt initiation of i.v. antiviral and i.v. antibiotic treatment could be necessary to treat these patients sufficiently when admitted with even mild signs of infectious disease [5].

In this case, the patient had a slowly growing thymoma following partial resection, and the irradiation therapy seemed well tolerated. The effect of the given chemotherapy was ignorable.

Interestingly, the effect of irradiation therapy on thymomas has, to our knowledge, not previously been reported as a factor for the development of Good's syndrome. However, it is well known that irradiation therapy can cause transient lymphocytopenia due to raised lymphocyte turnover. The background for the immunodeficiency in this case is probably the irradiation therapy since the immunodeficiency occurred shortly after the irradiation therapy. Furthermore, no clinical progression of the immunodeficiency has been seen more than 4 years after suspicion of Good's syndrome. T-lymphocyte count at 4 years after irradiation treatment is at a normal level, but the B-lymphocyte count remains extremely low. Substitution by intravenous Ig could probably help in the present case by reducing the number of upper airway infections [11]. Meanwhile, the patient has not been treated with intravenous Ig as infectious problems have been limited.

**Table 1.** Immunological values during 4-year follow-up

	Normal values	Before irradiation	3 months Jan 06	18 months Apr 07	35 months Sep 08	49 months Nov 09
Total leucocyte count, $\times 10^9/l$	3.0–9.0	5.9	5.4	3.1	3.9	5.6
Total lymphocyte count, $\times 10^9/l$	0.7–4.8	1.5	0.2	0.5	0.9	1.8
CD3+ T cells, % of lymphocytes	63–84	n.a.	60	35	62	77
CD4 T-cell count, $\times 10^9/l$	0.39–1.70	n.a.	0.04	0.16	0.24	0.78
CD45RAposROneg (virgin) CD4 T cells (% of CD4+ T cells)	4–58	n.a.	31%	n.a.	53%	73%
CD4/CD8 ratio	0.9–3.2	n.a.	1.3	1.2	1.0	1.6
CD19+ B cells, % of lymphocytes	6–18	n.a.	0	2	2	1
CD19 B-cell count, $\times 10^9/l$	0.09–0.57	n.a.	<0.01	0.01	0.03	0.02
Immunoglobulin G, g/l	6.1–14.9	n.a.	7.3	9.8	10.3	13.9
Immunoglobulin A, g/l	0.7–4.3	n.a.	1.19	1.34	1.43	1.38
Immunoglobulin M, g/l	0.39–2.08	n.a.	0.34	0.44	0.43	1.17

n.a. = Not analysed.

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