

# Role of Chemokine Signalling in the Pathogenesis of Good's Syndrome-Case Reports, Clinical Characterization from Single-Centre Perspective

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## Abstract

Good's syndrome (GS), is a rare condition defined as a coexistence of thymoma and hipogammaglobulinaemia. Involvement of central lymphoid organ prompts concept about perturbation in lymphocyte migration and differentiation. Cell homing to bone marrow compartment depends on the CXCR<sup>4</sup>↔CXCL<sup>12</sup> interaction. In this paper we describe two patients with GS-mild and severe form, presenting differences in the expression of CXCR<sup>4</sup> on cells in peripheral blood and bone marrow. Patient 1 (mild form): (i) Mild hipogammaglobulinaemia (IgG=150 mg/dL), (ii) Low count of peripheral B cells (14%, 60 cells/μL) and NK (18%, 77cells/μL); high level of T cells (93.3%, 4006 cells/μL), (iii) Moderate thymic enlargement (9 × 15 cm), (iv) CXCR<sup>4</sup> expression in BM 82.6% (20139/μL), 34% CXCR<sup>4</sup>+CD<sup>19</sup>+ (8289/μL). Patient 2 (severe form): (i) Severe hipogammaglobulinaemia (IgG=20 mg/dL), (ii) Absence of B and NK cells deficiency (in peripheral blood 0.4% i.e., 10/μL, and 6.17%-47.3/μL respectively), (iii) Severe thymic enlargement (20 × 25 cm) (iv) CXCR<sup>4</sup> expression in BM 46.3% (552/μL); 6.1%, CXCR<sup>4</sup>+CD<sup>19</sup>+ (174/μL). Interestingly, the bone marrow of patient with severe form of GS contained more CD<sup>10</sup>-positive B cells than BM of the patient with mild form (80% vs. 5.88% of B cells), but in former as well as latter a significant proportion of the total CXCR<sup>4</sup>-positive lymphocytes are negative for B cells marker (comparable: 48.1% and 53.1% respectively). In our patients a tenfold decrease in the CD<sup>4</sup>-positive γδ T cells (CD<sup>4</sup>+TCRγδ) counts was observed. Both cases went up fatal due to progression of nasopharyngeal cancer (mild form) and breast cancer (severe form). This data confirm that earliest B cell precursors, pre-pro-B cells and end-stage B cells, plasma cells require CXCR<sup>4</sup> ↔ CXCL<sup>12</sup> interaction. In contrast in GS weak expression of CXCR<sup>4</sup> in marrow precursors is source of B cell differentiation arrest on pro-B cell stage. The low level Nk and CD<sup>4</sup>+γδ T cells in Good syndrome is the new observation.

**Keywords:** Good's syndrome; Chemokine CXCR4 (fusin); B cell differentiation; NKT/NK ratio; CD4 γδ T cells; Thymoma; Immunosurveillance; Secondary malignancy

## Abbreviations:

GS: Good's Syndrome; CLP: Common Lymphoid Precursors; NK: Natural Killer Cell; NKT: Natural Killer T Cells; CXCL12: C-X-C Motif Chemokine 12; PBSF: Pre B Cell Growth-Stimulating Factor; CXCR: 4-C-X-C Chemokine Receptor Type 4; CD10 CALLA: Common Acute Lymphatic Leukemia Antigen; BM: Bone Marrow; MMPs: Matrix Metalloproteinase; EBV: Epstein Barr Virus; NHL: Non-Hodgkin Lymphoma; CVID: Common Variable Immunodeficiency; XLA: X-Linked Agammaglobulinemia; PRCA: Pure Red Cell Aplasia

## Introduction

The association between presence of a thymoma and hipogammaglobulinaemia was for the first time described in 1954 by Dr Robert Good who described a case of the rare immunodeficiency [1]. However initially classified as a form of predominantly humoral immunodeficiency T-cell abnormalities appeared to be an important component. The current classification of Good syndrome (GS), understood as a combined immunodeficiency, is based on

opportunistic infections, typically those dependent on T-cell decreased function, including mucocutaneous candidiasis, Pneumocystis jiroveci and herpes virus infection [2]. Unfortunately T-cell and thymic abnormalities in GS are poorly described; much of the literature is devoted to thymoma prognostic classification, its association with autoimmune diseases, paraneoplastic syndromes and secondary malignancy [3-5]. Nevertheless the cause and pathogenesis of this disorder are still unknown, however there are some evidences that the basic defects are bone marrow derived (BM) [6,7]. Coexistence of humoral and cellular deficiency, presence of thymoma in the context of observed bone marrow abnormalities prompted us to hypothesize that impaired migration of common lymphoid precursor (CLP) and further education may be a part of GS pathogenesis.

## Materials and Methods

### Patients characteristic

Six adult patients (age 30-50 years) with Good syndrome diagnosis between October 2010 and March 2016 were treated in our centre and qualified for immunoglobulin replacement therapy. 3 patients were excluded from evaluation by the long time between thymectomy and GS diagnosis (>1 years), 1 patient by lack of informed consent for draw the bone marrow sample. Fortunately 1 patient with mild symptoms,

residual adaptive immune response and 1 patient with most severe immunodeficiency, most aggressive thymoma and hipogammaglobulinaemia were enrolled for further immunological analysis at the time of thymectomy. Patients were given informed

consent for their sample analysis in accordance with the 5 Declaration of Helsinki. The clinical characteristics of the subjects are shown in Table 1.

Parameter	Patient 1 Mild Form	Patient 2 Most Severe Form	Clinical Significance
Clinical manifestation	Initially Lichen planus and alopecia areata, aplastic anaemia/PRCA	Initially serious sinopulmonary bacterial and fungal infections	Autoimmune disease is not essential, but infectious complication
Total WBC	15100 cells/ $\mu$ L	7100 cells/ $\mu$ L	
Initial IgG level before replacement and thymectomy	150 mg/dL	20 mg/dL	Yes (<200 mg/dL)
IgA, IgM	Not detected	Not detected	Yes
Specific antibody response	Residual (anti-HBs-29 IU/ml)	No	No C
Frequency of immunoglobulin substitution A	8-10 week	3 week	
Mean "plasma half-life" of IVIGB	60 days	20 days	
Delayed type hypersensitivity (DTH)	Negative	Negative	Yes D
Tumor mass ( $\varnothing$ cm) and WHO type	9 $\times$ 15 cm, AB	20 $\times$ 25 cm, B1	
Stage (Masaoka staging system)	I (curable by surgical resection)	II (resection+adjuvant therapy-radiation)	
Fatal complication (year after thymectomy)	Nasopharyngeal cancer EBV(3)	Chemoresistant breast cancer relapse (5)	Immunosurveillance abnormalities, escalated by thymectomy [3,17]

**Table 1:** Clinical data of 2 patients with extreme manifestations of Good syndrome; Crucial elements for differential diagnosis was described i.e., time between substitution with standard dose 0.2 gm/kg and moment when level <500 mg/dL; The time it takes for the IgG concentration to halve. Contrary to CVID, XLA residual humoral immune response may be observed as well as iso-haemagglutinin production. T cells abnormalities are qualitative rather (Table 2).

Immunoglobulin's levels were determined by turbidimetry (Olympus), leukocyte counts (WBC) analyses were done by the Sysmex Automated Hematology System. Flow cytometry was performed using a FACS Calibur flow cytometer (Becton Dickinson) and a count of lymphocyte subset was calculated by the frequency multiply the lymphocyte counts (Tables 2 and 3).

### Onset and course

**Patient 1-mild form:** 52-year old woman previously treated because of autoimmune background (lichen planus and alopecia areata) showed persistent nasopharyngeal *Candida* spp. and Epstein-Barr virus (EBV) infection, but without tonsils hypertrophy, lymphadenopathy and hepato-splenomegaly (typical mononucleosis presentation). She was admitted to the hospital because a mediastinal mass (9  $\times$  15 cm) was disclosed on a chest X-ray and suddenly increasing dyspnea. A biopsy evaluation confirmed presence of thymoma classified as an AB (mixed) type.

The patient despite the lack of IgA, IgM, and low IgG level (approx. 150 mg/dL) maintained a response to vaccination and had normal iso-haemagglutinin titer. DTH response was negative (Table 1). High

lymphocytosis (>4000/ $\mu$ L) corresponded to significant CD8 cells predominance (CD4/8 reversed ratio=0.18), low percentage and absolute count of B and NK cells. The  $\gamma\delta$  T cells level was normal (137/ $\mu$ L, normal range 4.5-3.18/ $\mu$ L i.e., 2.71-3.6%), but showing significant predominance of CD8 positive  $\gamma\delta$  T cells (CD8+TCR $\gamma\delta$ +) (Table 2) [6].

BM evaluation showed mild aplastic anaemia with high lymphocyte level, but accompanied by B cell maturation arrest (i.e., lack of early, mature) as well as low CD10 and high CXCR4 expression. Majority of CXCR4 positive lymphocytes are negative for B cells marker. Cytometric evaluation was summarized in Table 3. After thymoma resection bronchiolitis obliterans, mucosal candidiasis and atypical EBV infection gradually developed without B cells increase and lymphadenopathy (data not shown). No infection by encapsulated bacteria was observed. Unfortunately 3 years later the initial EBV infection with exudative pharyngitis followed by nasopharyngeal cancer at the same place. The patient died 6 weeks later after chemotherapy as a result of severe fungal pneumonia.

**Patient 2-most severe form:** 46-year old woman, 3 years after radical left breast cancer therapy (T1N0M0), had been often treated because of serious, recurrent sino pulmonary infections caused by encapsulated bacteria and fungi. She was suspected of having Hodgkin diseases because of the enlargement of mediastinal shadow in radiograms.

Presence of huge mass (20 × 25 cm) was confirmed by CT scans, biopsy evaluation classified the lesion as B1 thymoma (WHO B1, lymphocyte-rich). Laboratory evaluation disclosed very low level of immunoglobulins: IgG (20 mg/dL) with absence of IgA, IgM, isohaemagglutinins as well as specific antibody response and decreased DTH response was negative (Table 1). Despite the presence of lymphopenia (total lymphocytes <1000/ $\mu$ L) small content of B cells (0.4%) in the peripheral blood was observed, the NK level was comparable low, but CD4/8 ratio-higher (0.39) (Table 2). A higher percentage of  $\gamma\delta$  T cells were not observed either. Alike CD4 (+) form residual portions of peripheral, marrow and intestinal  $\gamma\delta$  T lymphocytes [6]. Others parameters are summarized in Table 2. In BM evaluation very low CXCR4 expression coexisted with high CD10. It

correlate to B cell differentiation arrest on pro-B cell stage (Table 3) with comparable to patients 1 absolute number (405 and 415/ $\mu$ L respectively), and lower level of cells in next steps of maturation B cells (0.2% CD19<sup>+</sup>CD20<sup>+</sup>).

Immunoglobulin replacement therapy gave the temporary improvement the sinopulmonary status, but chronic diarrhea developed as a result of an opportunistic intestinal infection. Unfortunately after thymectomy the humoral immune response and peripheral B cells level decrease was deeper than NK, NKT and T cells (Figure 1) but NKT/Nk ratio was reversed in first year. Five years after thymectomy fatal chemoresistant breast cancer relapse was observed.

peripheral lymphocytes	Mild form	Most severe form	Normal value [6]	Clinical significance
CD3 <sup>+</sup>	4006/ $\mu$ L (93.3%)	624/ $\mu$ L (81.5%)	1496–1700/ $\mu$ L -70.50%	
CD3 <sup>+</sup> CD4 <sup>+</sup>	589/ $\mu$ L (13.7%)	177/ $\mu$ L (23.1%)	940–1087/ $\mu$ L -44.83%	
CD3 <sup>+</sup> CD8 <sup>+</sup>	3172/ $\mu$ L (73.8%)	446/ $\mu$ L (58.1%)	606–715/ $\mu$ L -28.77%	
CD16 <sup>+</sup> 56 <sup>+</sup>	77/ $\mu$ L (1.8%)	47.3/ $\mu$ L (6.17%)	50-407/ $\mu$ L (11.4%)	Yes A ↓↓
CD3 <sup>+</sup> 56 <sup>+</sup>	215/ $\mu$ L -5%	92.8 $\mu$ L (12.1%)	253-318/ $\mu$ L B -12.87%	
NKT/NK	2.79	1.96	1.12	Yes C
CD19	60/ $\mu$ L (1.4%)	10/ $\mu$ L (0.4%)	90-660/ $\mu$ L (13.1%)	Yes
TCR $\gamma\delta$	137/ $\mu$ L (3.2%)	29 (3.9%)	4.5-318/ $\mu$ L (3.13%) <sup>6</sup>	Yes D
TCR $\gamma\delta$ <sup>+</sup> CD4 <sup>+</sup>	2.14/ $\mu$ L (0.05%)	0.15/ $\mu$ L (0.02%)	3.7-5.2/ $\mu$ L (0.04%)	Yes ↓↓↓ E
TCR $\gamma\delta$ <sup>+</sup> CD8 <sup>+</sup>	90.6/ $\mu$ L (2.11%)	13.85/ $\mu$ L (1.81%)	0.3-143/ $\mu$ L -0.84%	Yes E
TCR $\gamma\delta$ <sup>+</sup> CD4 <sup>-</sup> CD8 <sup>-</sup>	44.22 (1.03%)	15.92/ $\mu$ L (2.08%)	41.8–58/ $\mu$ L (2.22%) [6]	
CD4/8 for TCR $\alpha\beta$ ( $\gamma\delta$ )	0.18 (0.02)	0.39 (0.01)	1.2-1.5 (0.05)	Yes E

**Table 2:** Cytometric analysis of peripheral lymphocytes (membrane expression): Absolute values are expressed as cells/ $\mu$ L; Normal value is presented in 95% confidence interval of absolute and median of relative (%) numbers of cells in lymphocyte subset<sup>6</sup>; the level of CD16+56+ Natural Killer (NK) cells (marrow origin) is lower than median value in common variable immunodeficiency (CVID) (108/ $\mu$ L, 7,5%) and X-linked agammaglobulinemia (XLA) patients (139/ $\mu$ L, 11%)[19]; by age group 162,6 and 263,9/ $\mu$ L respectively; Physiologically absolute NK and CD3+56+ Natural Killer T cells (NKT) number and percentage are comparable, but GS patients show lower Nk level; Contrary to other combined immunodeficiency  $\gamma\delta$  T cells level in GS is not elevated; Inverse CD4/8 ratio for Good's syndrome (GS) is typical. In healthy donor CD4+ $\gamma\delta$  is approximately 5-fold less than CD8+ $\gamma\delta$  (estimated CD4/8 $\approx$ 0, 19) [6], but lower CD4 $\gamma\delta$  level is observed in the patients with Good Syndrome.

**BONE MARROW (BM)**

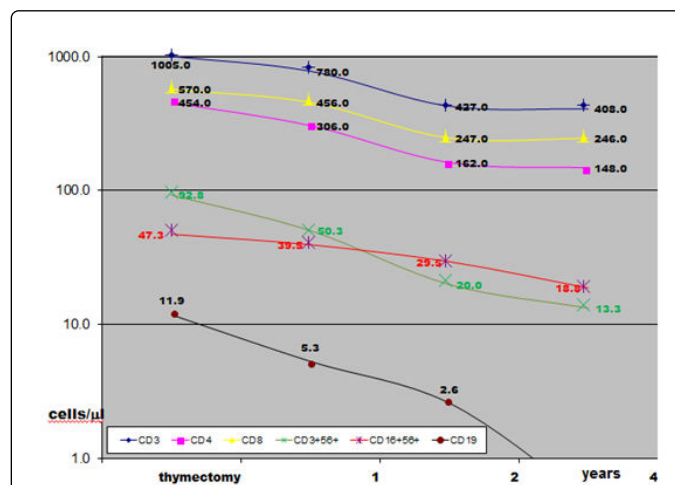
	Mild form	Most severe form	Clinical significance
<b>Lymphocytes (PRCA/aplastic anemia)</b>	33.4% (24382/ $\mu$ L)	4.8% (2850/ $\mu$ L)	No
<b>BM CXCR4</b>	87.2%	54.2%	
<b>Expression CXCR4 on lymphocytes</b>	82.6% (20139/ $\mu$ L)	19.4% (552/ $\mu$ L)	
<b>CXCR4+19+ (%lymphocytes)</b>	34% (8289/ $\mu$ L)	6.1% (174/ $\mu$ L)	
<b>Expression CD10 on lymphocytes</b>	0.1% (24/ $\mu$ L)	11.38% (324/ $\mu$ L)	
<b>CD10+ [%CD19+]B</b>	5.88%	80%	
<b>B cells differentiation arrest</b>			Yes
(subsequent steps of maturation cells/ $\mu$ L (% lymphocytes))			(on proB cell stage)
<b>CD19+ 20(-)C</b>	414/ $\mu$ L (1.7%)	405/ $\mu$ L (14.2%)	
<b>CD19+CD20+</b>	24/ $\mu$ L (0.1%)	5.7/ $\mu$ L (0.2%)	
<b>CD19+22+ (early and mature)</b>	36.5/ $\mu$ L (0.15%)	8.55/ $\mu$ L (0.3%)	
<b>CD20+CD23+ (transitional+newly emigrated +activated B cells)</b>	48/ $\mu$ L (0.2%)	<1/ $\mu$ L (0.03%)	

**Table 3:** Clinical significance of bone marrow abnormalities observed in patients with Goods Syndrome and B cells differentiation arrest; Physiologically CD10 is expressed both in CD34+CXCR4+ and CD34+CXCR4- B cell progenitors, while only CD34+CXCR4+ cells were positive for CD19 [9]; In GS inverse correlation CD10 and CXCR4 expression was observed: a significant proportion of the total CXCR4-positive lymphocytes are negative for B cells marker (CD19, CD10); pro-B cells that are CD19 positive yet still CD20 negative.

## Discussion

In the initial description by Good and Varco now known as Good Syndrome thymoma was believed to be secondary lesion to hipogammaglobulinaemia. Although it was later postulated that in fact thymic pathology was primary leading to hypogammaglobulinemia, the absence of B cells in peripheral blood and pre-B cells in bone marrow was never fully explained.

One concept assume that thymoma is a consequence of the other complications, like central tolerance defects and the marrow autoimmune processes (aplastic anaemia or pure red cell aplasia PRCA) [5,7], therefore block of B cells development [8]. On the contrary, a patient with mild GS had a significantly higher level of T cells (especially in bone marrow) than those with severe grade, but at the same maturation arrest pro-B cell precursors count was comparable (414 vs. 405/ $\mu$ L, Table 2). Follow up revealed that the surgical excision of thymoma results neither IgG nor B/Nk cell count increase, while induces permanent decrease of all subpopulation of T cells during 4 year observation (Figure 1). Therefore association between thymoma and hipogammaglobulinaemia seems not to be a simple consequence of the thymoma dependent decreased immune function, but rather abnormal differentiation of lymphoid precursor cell subset in BM, as possibly observed decrease of B cells NK cells level (Table 2). B cells in patients with severe form of GS were defective and failed to produce normal amount of immunoglobulin even when the influence of T cells was inhibited (for example by immunosuppressive cyclosporine therapy as PRCA [7]); further CD3+56+/CD16+56+ (NKT/NK) ratio was high and stayed reversed 2 years after thymectomy (Figure 1). The CD3+56+ natural killer T (NKT) subset is a minor subpopulation of T cells, so are thymic in origin, but most of CD16+56+ natural killer (NK) cell development occurs in the bone marrow.



**Figure 1:** Deficiency in circulating lymphocyte subsets in Good's Syndrome intensified after surgical intervention (data presented as absolute cell count [cells/ $\mu$ L]); initially deficiency in circulating B cells and natural killer cell (NK i.e., CD16+56+) subsets (marrow origin) is deeper than T cells and NKT (thymic origin). In first year after thymectomy the NKT/NK ratio was reversed, but Nk cells decrease was still been observed. On the contrary decrease in B cells count was 5 times as high as it was in the T cells. The deep NK deficiency is observed also after thymectomy.

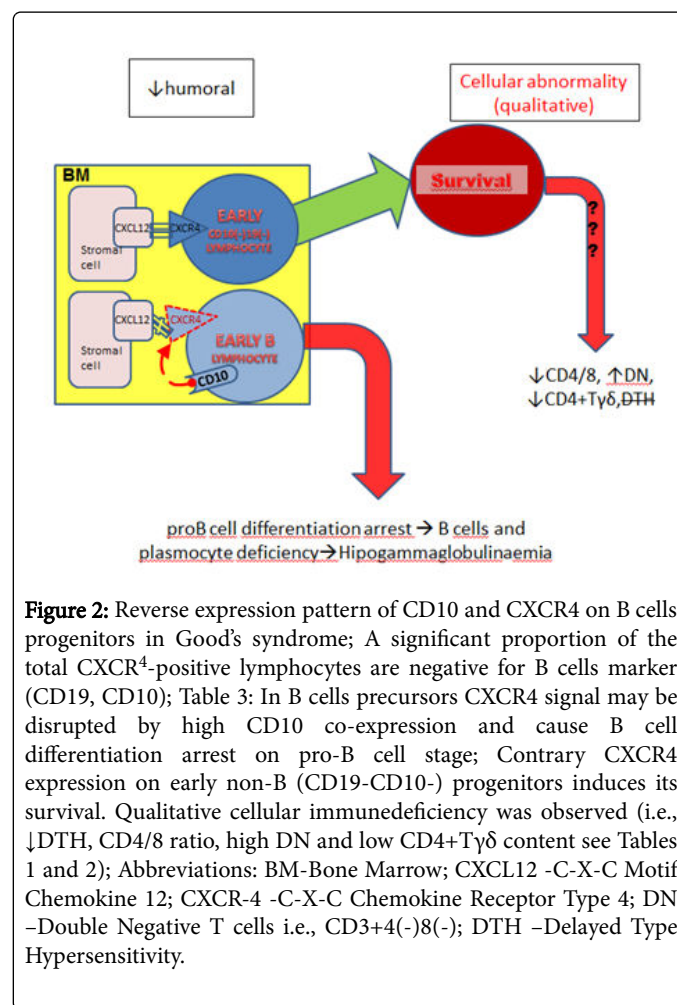
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PRCA) [5,7], therefore block of B cells development [8]. On the contrary, a patient with mild GS had a significantly higher level of T cells (especially in bone marrow) than those with severe grade, but at the same maturation arrest pro-B cell precursors count was comparable (414 vs. 405/ $\mu$ L, Table 2). Follow up revealed that the surgical excision of thymoma results neither IgG nor B/Nk cell count increase, while induces permanent decrease of all subpopulation of T cells during 4 year observation (Figure 1). Therefore association between thymoma and hipogammaglobulinaemia seems not to be a simple consequence of the thymoma dependent decreased immune function, but rather abnormal differentiation of lymphoid precursor cell subset in BM, as possibly observed decrease of B cells NK cells level (Table 2). B cells in patients with severe form of GS were defective and failed to produce normal amount of immunoglobulin even when the influence of T cells was inhibited (for example by immunosuppressive cyclosporine therapy as PRCA [7]); further CD3+56+/CD16+56+ (NKT/NK) ratio was high and stayed reversed 2 years after thymectomy (Figure 1). The CD3+56+ natural killer T (NKT) subset is a minor subpopulation of T cells, so are thymic in origin, but most of CD16+56+ natural killer (NK) cell development occurs in the bone marrow.

GS derived T cells and intestinal lymphocytes show similar phenotype pattern: Large proportion of CD8 and high CD4-8- content of T cells (Table 2). Both in bone marrow and peripheral blood CD4/8 ratio were about 0.5 while delayed DTH response was negative. On the contrary to ESID criteria of combined immunodeficiency the  $\gamma\delta$  T cells level in our patients were normal but the CD4-positive  $\gamma\delta$  T cells (CD4+TCR $\gamma\delta$ ) count in healthy adult subjects was above ten times higher than in the our patients (Table 2) [6]. The crucial role of CXCR4 receptor for lymphocyte B development depends on effective CXCL12 binding that is driving cell homing. Direct evidence shows CD34 (+) CXCR4 (-) B cells precursors express CD10 in much higher degree than CD34 (+) CXCR4 (+) B cells subset [9]. In addition, most of the earliest B cell precursors, pre-pro-B cells and end-stage B cells, plasma cells require CXCL12 [10]. Therefore CXCL12, formerly called pre-B-cell growth-stimulating factor (PBSF), are essential for B-lymphocyte expansion and bone marrow colonization. Weak interaction between CXCL12 and its ligand CXCR4 on B cells precursors (low expression observed here) results in B and possibly NK cells differentiation arrest (Tables 2 and 3). B cell differentiation arrest is visible when we compare cell counts in subsequent steps of maturation in bone marrow (Table 3): More than 400/ $\mu$ L pro-B cells were observed, but CD20+ or CD22+ hundreds less. To our knowledge, this is the first report in GS. Reverse expression pattern of CD10 and CXCR4 observed here is probably crucial novelty (Figure 2). CXCR4 showed a reverse pattern to CD10: a significant proportion of the total CXCR4-positive lymphocytes are negative for B cells marker (CD19, CD10) (i.e., 48.1% and 53.1% respectively, Table 3). The phenomenon seems to be universal; reduced expression of the CXCR4 is responsible for carcinoma cells migration and metastasis of hepatocellular carcinoma [11]. CD10 is up regulated in metastatic melanomas, rare phenomenon in primary melanomas [12]; was found significantly higher in metastatic than in primary tumors [13]. Mantle cell lymphoma with aberrant expression of CD10 was described as a more aggressive [14].

Primary immunological abnormalities, observed here, are due to a lack of plasma cells and B cells differentiation, lymph nodes and tonsils atrophy, lack of antibody synthesis (all isotypes). The course of EBV infection in patients 1 (mild form) with cellular immunodefect and low level target B cells (intensified after thymectomy, Figure 1) are probably source of massive replication in nasopharyngeal epithelium

and cancer. UL16-binding protein-4 (ULBP4) expressed not only on human tumor cells, but also on EBV-infected cells is a ligand for both TCR $\gamma\delta$  and NKG2D [15]. In GS low level of NK, and CD4+  $\gamma\delta$  T cells may be source of both: low immune surveillance of tumor development and weak clearance of viral infection. In our patients contrary to myasthenic ones [16] innate NK/NKT immunodisturbance is not normalized, but even escalated after thymectomy (Figure 1). Significantly lower IgG level, percentage of peripheral blood B lymphocytes, CD4/CD8 ratio and expression of CD28 in thymectomized patients was described elsewhere [17] and may be source of diagnostic problem after thymectomy [18,19].



GS is rare combined immunodeficiency, but pathological characteristic is difficult because thymectomy usually precede immunological examination, coexistence between thymoma and other abnormalities may be result of immunodefect after thymectomy and opportunistic infections. B and T cell immunoregulation in thymoma patients is sometimes referred to as GS [4,20], but it represents rather a different disease with distinct etiology and pathogenesis where B cell lymphopenia due to differentiation arrest seems to be crucial. Weak definition of GS is source misconception: severe hipogammaglobulinaemia or decrease of all isotypes is not sometimes observed [4,20], the humoral type spectrum of opportunistic infections was therefore described [20].

This study has obvious limitations because of single center and casuistic nature (3 patients was disqualified, only 2 cases preceding

thymectomy were characterized in our center) but study of larger scale is difficult without strict definition of GS, after thymectomy and serious complications. The crucial clinical and immune parameters still has to be established as diagnostic criteria for further evaluation and differentiation from other immunodeficiency with hypogammaglobulinaemia (Good's syndrome shows lower level of NK cells and portends a poorer prognosis than XLA, CVID) (Figure 1, Tables 1 and 2) [19].

## Conclusions

Although physiologically CD10 is expressed both in CXCR4+ and CXCR4- B cell progenitors [9] CXCR4-deficiency on B cell and its differentiation arrest cause of mature B and plasma cells absence, therefore humoral immunodeficiency -IgM, IgA and IgG class, which are hallmark of GS (Tables 1 and 2, Figure 2). Low level Nk and "helper"  $\gamma\delta$ T cells demands appropriate observation and further research.

## Consent for Publication

Written consent to publish this report was obtained from the patients.

## Availability of Data and Materials

The datasets supporting the conclusions of this article are included within the article and its additional files (Tables 1-3; Figures 1-2).

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## Authors' contributions

P.Z. collects clinical data, G.D.-cytopathological and histopathological A.K.K. and A.G.-microbiological analysis. A.K.K. improved of the English language all authors participated in drafting and editing the manuscript. All authors read and approved the final manuscript.

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