J Clin Immunol (2013) 33:520–525
DOI 10.1007/s10875-012-9833-6

ORIGINAL RESEARCH

Inflammatory Bowel Disease and T cell Lymphopenia in G6PC3 Deficiency

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Received: 9 October 2012 / Accepted: 30 October 2012 / Published online: 20 November 2012

Abstract
Purpose G6PC3 deficiency presents as a complex and heterogeneous syndrome that classically associates severe congenital neutropenia with cardiac and urogenital developmental defects. Here we investigate the findings of T cell lymphopenia and inflammatory bowel disease in a child with G6PC3 deficiency due to compound heterozygous mutations in intron 3 (c.IVS3-1 G>A) and exon 6 (c.G778G/C; p.Gly260/Arg).
Methods Histological examination was conducted on all biopsy specimens. Immunophenotyping and lymphocyte proliferation assays were performed. Immunoglobulin levels and vaccine responses were measured.
Results The patient showed persistent global T cell lymphopenia, with only 8 to 13 % of thymic naive $CD31^{+}CD45RA^{+}$ cells among CD4 T cells (normal range 27–60 %). Proliferation assays and vaccine responses were within normal limits. The gastrointestinal inflammatory lesions were very closely related to those of glycogen storage disease type 1b, with a Crohn's-like appearance but without granuloma or increased cryptic abscesses. The gastrointestinal disease responded to infliximab therapy. These findings were associated with a polyclonal hypergammaglobuliemia G.
Conclusion G6PC3 deficiency may present with inflammatory bowel disease and T cell lymphopenia. The diagnosis should thus be considered in a patient with chronic congenital neutropenia and gastrointestinal symptoms. Patients with confirmed disease should also undergo T cell phenotyping to rule out cellular immunodeficiency.

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Keywords G6PC3 · congenital neutropenia · inflammatory bowel disease · lymphopenia · G6PT · thymic naive

Introduction

Severe congenital neutropenia belongs to a heterogeneous group of diseases that is associated with life-threatening bacterial infections early in life. From a clinical point of view, they may be classified as isolated severe neutropenias without additional organ involvement (as seen with ELA2, WAS, HAX1 or GF11 mutations) or as congenital severe neutropenias associated with syndrome features (as seen in reticular dysgenesis, hypopigmentation syndromes, WHIM syndrome or glycogen storage disease type 1b (GSD1b)) [1].

Recently, a second congenital neutropenia syndrome that involved defective glucose metabolism was described, caused by biallelic mutations in G6PC3, the gene encoding glucose-6-phosphatase catalytic subunit 3 [2]. G6PC3 is the third glucose-6-phospatase subunit, which catalyzes the last step of glycogenolysis in the endoplasmic reticulum (ER). The first subunit (G6PC1) is expressed mainly in the liver, and its loss of function results in glycogen storage disease type 1a [3]. G6PC3, on the other hand, is expressed ubiquitously [4] and its deficiency does not result in glycogen storage disease presumably because the G6PC1 subunit is sufficient to regulate glucose metabolism in the liver. It does, however, regulate glucose homeostasis in neutrophils, which require a constant supply of glucose to function and survive. Neutrophils also show a greater demand for glucose when responding to immune threats due to increased mobility, phagocytosis, and reactive oxygen species (ROS) production [5]. It could also affect protein glycosylation within the ER [6]. Thus, loss of G6PC3 activity can deleteriously impact many functions as well as survival of neutrophils [3, 5].

Since the initial report, which identified 12 patients with a G6PC3 deficiency, a handful of cases have been described in the literature [2, 7–12]. Patients typically present with a complex syndrome that associates severe neutropenia with variable cardiovascular and/or urogenital developmental defects and increased visibility of superficial veins. In addition to these classical features, they may also display a wide array of other clinical findings with variable penetrance (such as intermittent thrombopenia, myopathy, proximal thumbs, and incomplete puberty). Here, we report the case of a young girl who was diagnosed with severe non-specific inflammatory bowel disease (IBD), T cell lymphopenia and hypergammaglobulinemia as manifestations of a G6PC3 deficiency. We discuss the ramifications of having a low naive T cell count that can also be part of the syndrome and how such a finding in a patient with chronic neutropenia should alert the physician to consider a diagnosis of G6PC3 deficiency.

Case Presentation

After an uneventful pregnancy, the first child of healthy non-consanguineous parents was born at term with congenital neutropenia and mitral valve insufficiency. A bone marrow examination revealed normal hematopoiesis with a normal 46 XX karyotype. At 6 months of age, she developed skin abscesses following vaccinations. Her skin was already striking, with a parchment-like appearance laced with numerous superficial veins. Over the next 5 years, the patient had recurrent otitis media and statural growth delay. Neutropenia had varied between 100 and 400×10^9/L since birth. At 6 years of age, she started experiencing recurrent abdominal pain and numerous large oral and genital aphthous ulcerations. Colonoscopy was performed at age 10 and showed a severe inflamed stricture at the right hepatic angle. She was started on granulocyte colony stimulating factor (G-CSF), 5 μg/kg, three times a week, as well as 5-aminosalicylates and prednisone.

Although her aphthous ulceration resolved, she developed progressive sub-occlusive gastrointestinal symptoms and right hemicolectomy was performed at age 13. At that time, a complete blood revealed decreased total lymphocyte counts (600 cells/mm^3, RV is 1,500–5,100 cells/mm^3). Immunoglobulin (Ig) G levels were also elevated at 23.40 mg/dl (RV 5.29–15.21) (Table I).

Despite prophylaxis with G-CSF and trimethoprim-sulfamethoxazole (TMP-SMX), she experienced multiple episodes of skin abscesses and two episodes of enterocutaneous fistulae over the following years. Her neutropenia showed very limited response to G-CSF. Lymphopenia persisted, most often with cell counts of less than 1,000/mm^3.

Infliximab was started at age 18 and has been well tolerated. Since then, her gastrointestinal symptoms have remitted completely and a control colonoscopy has shown no evidence of disease activity.

Molecular analysis excluded mutation in the SBDS gene, the cause of Shwachman-Diamond syndrome. Based on the findings of chronic congenital neutropenia, abnormal venous pattern and congenital heart defect, a diagnosis of G6PC3 deficiency was suspected, despite the atypical findings of inflammatory bowel disease, T cell lymphopenia and hypergammaglobulinemia.

After informed consent, blood was obtained for genetic analysis from the proband and her parents. Approval for this study was obtained from the CHU Sainte-Justine Ethics Committee.

Table I Immunologic Work up of the patient between 12 and 18 years of age

	Patient	Normal values [a]
White-cell count		
Leucocytes (cells/mm^3)	1,200–2,160	4,500–11,000
Granulocytes (cells/mm^3)	200–1,100	1,800–7,000
Lymphocytes (cells/mm^3)	600–1,300	1500–2,800
Monocytes (cells/mm^3)	300–400	0–900
Eosinophils (cells/mm^3)	0	0–400
Immunoglobulins		
IgG (mg/dl)	22.40–31.50	5.29–15.21
IgA (mg/dl)	1.17–1.34	0.65–4.02
IgM (mg/dl)	1.83–2.40	0.22–2.82
IgE (KU/L)	6–17	0–100
IgG2 (mg/dl)	6.00–9.74	0.44–4.95
Lymphocyte population		
CD3$^+$ T cells (/mm^3)	348–962	1,038–1,986
CD4$^+$ T cells (/mm^3)	192–481	598–1,255
CD8$^+$ T cells (/mm^3)	96–299	272–753
CD31$^+$ CD45RA$^+$/CD4$^+$ (%)	8–13	27–60
TCR αβ$^+$/CD3$^+$(%)	80–86	85–95
TCR γδ$^+$/CD3$^+$(%)	14–20	5–15
CD56$^+$ CD3$^-$ NK cells (/mm^3)	68–148	76–343
CD19$^+$ B cells (/mm^3)	120–221	123–486
CD27$^+$/CD19$^+$(%)	15–26	10–35
T cell proliferation[b] (CPMx10^3)		
Unstimulated (day 4)	1.1	≤2.0
Phytohemagglutinin (2 μg/ml)	42	≥40
Anti-CD3 (OKT3) (50 ng/ml)	36	≥20
Unstimulated (day 6)	0.2	≤2.0
Tetanus toxoid(1:250)	15	≥15

[a] The reference range and laboratory values are provided for the patient's age group. The reference range encompasses values between the 5th and the 95th percentile for the 12 to 18 year age group

[b] Counts per minute of incorporated [3H] thymidine for the patient and control subject

Materials and Methods

Immunological Investigation

The following monoclonal antibodies (mAb) were used in immunofluorescence studies: anti-CD3: Leu4, anti-CD4: Leu 3a, anti-CD8: Leu 2a, anti-CD19: HIB, anti-CD31: WM59, anti-CD56: MY31, (Becton Dickinson, San Diego, CA), anti-TCR αβ: BMA031, anti-TCR γδ: IMMU 510, anti-CD45RA: ALB11, anti-TCRBV1: BL37.2, anti-TCRBV: MPB2D5, anti-TCRBV3: CH92, anti-TCRBV8: 56C5.2, anti-TCRBV14: CAS1.1.3 and anti-TCRBV17: E17.5 F3.15.13, (Beckman Coulter, Mississauga, Canada). Fluorescence staining was done with phycoerythrin (PE)-, fluorescein isothiocyanate (FITC)- or allophycocyanin (APC)-conjugated mAbs on whole blood.

Cells were analyzed on a FACSCanto flow cytometer (Becton Dickinson) using FACSDiva software. Lymphocyte proliferation assays were performed as described previously [13]. Serum Ig concentrations were determined by nephelometry, and serum antibody concentrations were determined by ELISA. The polyclonality of Igs was examined by immune electrophoresis.

Gastrointestinal Pathology

The histological examination was conducted on all specimens (surgical or biopsy) obtained during a period of 4 years. Sections were stained with hematoxylin phloxine saffron (HPS). Immunohistochemical evaluation was conducted on the following antigens: IgG4 (HP6025 monoclonal mouse, Invitrogen, Camarillo, CA, USA), CD15 mouse monoclonal antibody (Ventana Medical Systems Inc., Tucson, AZ), CD3 rabbit polyclonal antibody and IgG (Cell Marque, Rocklin, CA, USA). Immunohistochemistry was performed on paraffin-embedded sections using a Benchmark XT automated immunostainer (Ventana Medical Systems Inc.) according to the company's protocol with minor modifications.

IgG4 positive plasma cells were counted per high power field (hpf, 400X magnification) in the most densely populated area of the slide (mild, 5–10/hpf; moderate, 11–30/hpf; marked >30/hpf) [14].

Sequencing Analysis of Genomic DNA

DNA was extracted from Blood using a QIamp DNA Mini Kit (QUIAGEN) following the manufacturer's recommended protocol. Polymerase chain reaction (PCR) amplification of all exons and exon-intron boundaries of the human *G6PC3* gene was performed as described previously [2]. Subsequent DNA sequencing was performed on an ABI3130XL Genetic Analyzer (Applied Biosystems, Darmstadt, Germany).

Results

Immunological Investigation

Phenotypic analysis of the patient's lymphocyte subsets, performed between 12 and 18 years of age, showed persistent T cell lymphopenia involving CD4$^+$ and CD8$^+$ lymphocytes (Table I). B and NK cell numbers were within the normal. Most T cells expressed TCRαβ (80 to 86 %) (Table I). The Vβ usage by the CD4$^+$ and CD8$^+$ T lymphocytes, studied by immunofluorescence, was diverse and normal for all tested Vβ segments (data not shown). Naive thymic CD4$^+$ T cells, as defined by the coexpression of CD31 and CD45RA, were present in

low proportions in the patient at 12 years of age (13 % among $CD4^+$ T lymphocytes) and had decreased to 8 % 4 years later (normal range = 27–60 %). A normal proportion of memory B cells (15 %; normal range = 10–35 %) exhibited a memory phenotype as defined by the expression of CD27. The lymphocyte proliferation response to mitogens (Pha and OKT3) and to a specific antigen (tetanus toxoid) was normal (Table I).

The hyper immunoglobulinemia G was constant, while IgA and IgM levels were normal. No monoclonality was detected within the IgG fraction and post-vaccination antibody titers (rubella, mumps, measles, tetanus, diphtheria, varicella) were within the protective range (Table I).

Apart from the lymphopenia, the main anomaly observed was a low proportion of naive thymic CD4 lymphocytes, suggesting an impaired thymic output.

Gastrointestinal Pathology

Macroscopically, the disease involved the terminal ileum in association with the right colon. A terminal obstruction was observed in the last five centimeters of the ileum. Around the stenosis the mucosa appeared hyperemic with few pseudopolyps present, and fat encircling the stenosis was fibrous. Distally from the obstruction, the bowel, including the appendix, was normal.

Colonic architectural changes were associated with fissuring ulcers extending through the bowel wall until the muscular layers, inflammatory polyps, hyperplastic lymphoid aggregates in mucosal, submucosal and subserosal adipose tissue layers, particularly around the vessels, as well as extensive fibrous changes in adipose tissue (Fig. 1). Hypertrophic nerve fibers were seen in the myenteric plexus. Fissures contained acute inflammatory cells such as neutrophils ($CD15^+$ cells), eosinophils, lymphocytes, and polytypic plasma cells in which IgG4 was moderately increased (13/hpf), as well as a granulated tissue lining with conspicuous pale histiocytic cells. The epithelium ranged from completely normal to acutely damaged, chronically damaged or regenerative. In areas of the colon affected by active disease, the normal architecture of the crypts and villi was distorted. This architectural distortion was characterized by crypt abscesses and glandular branching, dilatation, or elongation. The epithelium lining the distorted glands often appeared hyperplastic with Paneth cell metaplasia.

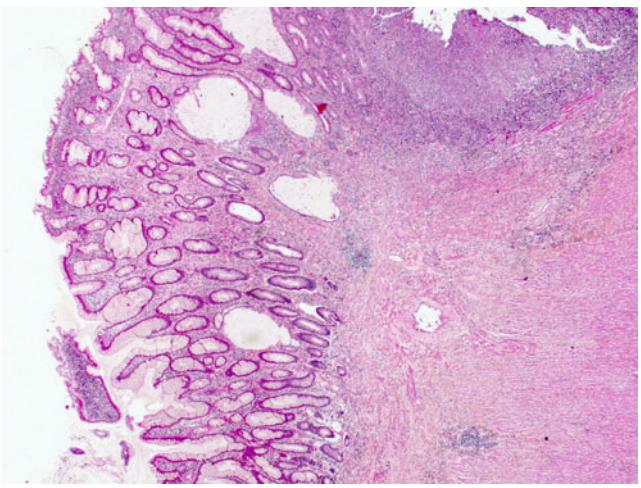

Fig. 1 Hematoxylin and eosin staining at 2.5X showing hyperplasic lymphoid aggregates in mucosal, submucosal tissue layers, as well as extensive fibrous changes in adipose tissue

The appearance of the left colon and rectal mucosa was normal. The upper tract was not studied. Histological examination thus revealed a Crohn's-like appearance but specific granulomatous lesions were never observed.

Gene Sequencing

The G6PC3 gene was sequenced and revealed compound heterozygous mutations. One novel mutation was located in intron 3 (c.IVS3-1 G>A) and the other previously reported [15] mutation in exon 6 (c.G778G/C; p.Gly260/Arg).

Discussion

We describe a patient with a compound heterozygous mutation in the G6PC3 gene who presented with severe IBD and thymic naive T cell lymphopenia in addition to the more classical features of the disease. These unusual findings, which have not been previously reported in patients with a G6PC3 deficiency, may have a significant impact on the care of patients with this heterogeneous syndrome.

Thymic naive $CD4^+$ T cells, which are closely related to thymic emigrants, were greatly decreased in our patient. While thymic output seems to be impaired, the peripheral T cells displayed a diversified Vβ repertoire. Our study is the first to report on thymic naive T cells in G6PC3 deficient patients. Only one group had previously performed T cell subset analysis in G6PC3 deficient patients [9]. They had found a low number of total T cells in two siblings, both of whom died from severe respiratory distress at the age of 18 months. Both patients were found to have thymic hypoplasia.

The mechanisms leading to T cell and, more specifically, to thymic naive T cell lymphopenia in G6PC3-deficient patients are unclear. Lymphocytes appear relatively resistant to glucose deprivation. In an experiment by Botzug and colleagues, inhibition of glucose metabolism by 2-deoxyglucose did not increase apoptosis in $CD3^+$ T lymphocytes as it did in neutrophils from G6PC3-deficient patients [2].

Expression of CXCR4, which is dramatically increased in G6PC3-deficient neutrophils, was found to be expressed within the normal range in G6PC3-deficient T lymphocytes [12] and, thus, CXCR4 is unlikely to contribute to the

lymphopenia observed in G6PC3 deficiency as it does in the WHIM syndrome [17].

A more compelling hypothesis is that naive T cell deficiency results from structural defects in the thymus. Although there is only one report of thymic hypoplasia in G6PC3-deficient patients, this observation may easily go unnoticed unless specifically addressed in the first years of life. These patients frequently present with cardiac malformations and it would make sense for the thymus to be similarly affected. Dysorganogenesis in G6PC3 deficiency could result from stromal cell dysfunction as fibroblasts have been shown to be susceptible to stress-induced apoptosis similar to neutrophils. Thymic hypoplasia might impact thymic emigration and explain subsequent T cell lymphopenia and more specifically low $CD45RA^{+}CD31^{+}$ thymic naive T cell counts, as described for partial DiGeorge syndrome [18].

The low count observed in our patient did not result in opportunistic infection, even before TMP-SMX prophylaxis. However, as there is a very wide spectrum of severity with regard to organ malformation, one could also expect that thymic involvement would vary greatly between cases, as would T cell and thymic naive involvement.

Our results suggest that patients with G6PC3 deficiency should be screened for T cell immunodeficiency as this subgroup may have a significant impairment in cellular immunity. Also, the incidental finding of low T cells or low $CD31^{+}CD4^{+}$ naive thymic emigrants in a patient with chronic or congenital neutropenia should raise the suspicion of a G6PC3 deficiency.

Our study is also the first report describing the association of IBD with G6PC3 deficiency. Although not previously attributed to the disease, isolated cases from previous series did present with gastrointestinal symptoms suggesting that this is not just a coincidental finding [6, 10, 12]. We show that the gastrointestinal lesions of G6PC3 deficiency differ from Crohn's disease by the absence of granuloma and the severity of crypt inflammation. Clinical and pathological presentation of the IBD of G6PC3 deficiency resembles that found in GSD1b, a closely related congenital neutropenia syndrome caused by mutation in G6P translocase (G6PT).

G6PT mediates transport of G6P to the ER and is thus required for G6PC1 and G6PC3 activity [19]. GSD1b combines a glycogen storage disease (as seen with G6PC1 deficiency) with a severe congenital neutropenia [20]. Between 22 and 50 % of patients with GSD1b also present with IBD [21, 22]. In accordance with our patient, gastrointestinal disease is diagnosed at an average age of 8.7 years [21]. As with G6PC3 deficiency, they present a Crohn's-like disease with increased propensity to develop microabscesses but rarely with granulomas.

The novel mutation on intron 3 is located in a 3′ splice site. Although we cannot completely exclude the possibility that small amounts of a normal or abnormal protein would still be expressed, we can speculate that this mutation impairs mRNA transcription and prevents protein expression. Consequently, the protein expressed in the patient's cells would present the amino acid substitution Gly260/Arg encoded by the other allele. This mutation has been previously shown to be associated with the disease. [2, 11, 12, 16]. Interestingly, one report describes two siblings homozygous for this mutation who presented poor growth associated with malabsorption and intermittent abdominal pain. No T cell defects were described in association with this mutation so far.

Polyclonal hypergammaglobulinemia G that was observed in our patient has never been reported before in patients with G6PC3 deficiency. It probably relates to the IBD more than to the underlying mutation itself since polyclonal hypergammaglobulinemia is a common non-specific finding in chronic inflammatory diseases [23].

Our experience indicates that treatment of IBD in G6PC3 deficiency may be challenging. Our patient was resistant to standard treatment with prednisone or anti-inflammatory medication. However, we show that the anti-TNFα monoclonal antibody infliximab can be a very effective alternative to control gastrointestinal symptoms, as evidenced by the complete remission in our patient. Although not attempted here, another option reported to have a favorable gastrointestinal outcome in GSD1b is bone marrow grafting but this should be reserved for patients refractory to anti-TNFα therapy or with other indications [24].

In conclusion, we report a case of G6PC3 deficiency associated with naive T cell lymphopenia and severe non-specific IBD. The IBD diagnosed in G6PC3 deficiency was closely related to that of GSD1b and responded to anti-TNFα therapy. The finding of T cell and naive thymic T cell lymphopenia is thought to result from thymic hypoplasia and it should orient the diagnosis in a patient with chronic congenital neutropenia. Patients with confirmed disease should also undergo T cell phenotyping to rule out cellular immunodeficiency.

Conflicts of interest None of the authors has any potential financial conflict of interest related to this manuscript

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