# A case of SLC29A3 spectrum disorder - unresponsive to multiple immunomodulatory therapies

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**Abbreviations**

SLE- Systemic lupus erythematosus

RDD- Rosai-Dorfmann disease

FHC- Faisalabad histiocytosis

SHML- Sinus histiocytosis with massive lymphadenopathy

PHID- Pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome

CRP- C-reactive Protein

DMARD- Disease Modifying Anti-Rheumatic Drug

**Key Words**

SLC29A3 spectrum disorder

H syndrome,

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To the editor,

Histiocytosis are a group of rare disorders caused by an excessive number of histiocytes which phagocytose other cells. Their pathophysiology remains uncertain and their treatment non-specific. Rosai-Dorfmann disease (RDD) is a particular form of histiocytosis which presents with massive lymphadenopathy, it can be familial or occur sporadically. The histiocytosis-lymphadenopathy plus syndrome comprises features of four histiocytic disorders (#OMM 602782):

1. Faisalabad histiocytosis (FHC)
2. Sinus histiocytosis with massive lymphadenopathy (SHML), also known as familial RDD
3. H syndrome
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These conditions were once thought to be separate disorders; however in light of the overlapping features and shared genetic cause, they are now considered to be part of the same disease spectrum. They are all caused by homozygous or compound heterozygous mutation in the *SLC29A3* gene on chromosome 10q22, hence they are also called SLC29A3 spectrum disorders (1-6). Their clinical features are summarised in Figure 1.

The *SLC29A3* gene encodes equilibrative nucleoside transporter 3(ENT3). ENT3 belongs to a family of nucleoside transport proteins which play key roles in nucleoside metabolism. ENT3 is ubiquitously expressed, particularly on endosomal and mitochondrial membranes (7). *SLC29A3* mutations typically cause altered stability of the ENT protein (8). SLC29A3-null mice develop lysosomal accumulation of nucleotides and altered macrophage function (9), which provides a molecular basis for some clinical aspects of the SLC29A3 spectrum disorders, however it does not explain the entire phenotype.

Information on the gross clinical phenotype of SLC29A3 spectrum disorders has been described. However information on the immunological abnormalities and management of these disorders remains sparse. We present the case of a 21-year-old female patient with SLC29A3 spectrum disorder whose symptoms have been refractory to a number of immunomodulatory therapies.

The patient is from a consanguineous marriage (her parents are first cousins). She initially presented at the age of two with a self-limiting sharply demarcated telangiectatic rash. Subsequently, she developed a number of ill-defined problems including dactylitis, arthralgia and debilitating fatigue. In her early teenage years, she was managed with a working diagnosis of Systemic Lupus Erythematosus (SLE) in view of her troublesome rash; progressive alopecia, microscopic haematuria and a positive anti-double stranded DNA antibody titre. The diagnosis of SLE did not however unify her other symptoms and clinical features (Table 1). This included RDD which initially presented at the

age of 9 with a large painless right mandibular mass. Excision of the mass showed massively enlarged lymph nodes which had features in keeping with RDD on microscopic examination (Fig.2).

Her most troublesome symptoms were cutaneous. At the age of 11 she developed crusted purple plaques affecting the pinnae of her ears, forearms and shins. The gross clinical appearance of the rash was consistent with discoid lupus, however biopsies confirmed lichen planus, with no suggestion of SLE. More recently the patient has developed a more diffuse rash consisting of widespread nodules, histopathology showed a mixed infiltrate of enlarged histiocytes containing phagocytosed lymphocytes. The histiocytes show a CD68+,CD163+,S100+,CD1a- immunophenotype in keeping with Rosai-Dorfmann disease.

Blood work has invariably shown a balanced lymphopenia affecting T and B cells with normal numbers of NK cells. Further B cell analysis showed reduced class-switched memory compartment. Phytohaemagglutinin induced T cell proliferation was normal (Table 2). The patient initially had a polyclonal gammaglobulinaemia, she subsequently developed an IgG kappa paraproteinaemia (Figure 3) as well as a persistently raised C-reactive protein (CRP) between 30-50mg/l.

In view of her lymphadenopathy, and autoimmune features, a diagnosis of autoimmune lymphoproliferative syndrome (ALPS) was also considered. However, further studies including functional apoptosis assays, analysis of double negative T cells, serum levels of B12 vitamin, soluble Fas ligand and Intreleukin-10 were all normal. A diagnosis of autoimmune polyendocrine syndrome type 1 was another diagnosis under consideration, but genetic test for *AIRE* gene mutations was negative. Her lymphadenopathy, hyperpigmentation and pedigree suggested Gaucher's disease. However, normal glucocerebrosidase tests excluded this lysosomal disorder.

The diagnosis of a SLC29A3 spectrum disorder was made with the aid of whole exome sequencing. She was found to have homozygous mutation in the splice donor site in the second intron of *SLC29A3* (NM_018344.5:c.300+1G>A). Considering her clinical features and the fact that this variant has been previously described in a family with FHC [2], it was concluded that this mutation is the most likely cause of her condition.

Multiple therapies were trialled to manage the patient's cutaneous and musculoskeletal symptoms. She had a course of hydroxychloroquine, ciclosporin, methotrexate, thalidomide and mycophenolate for her skin. There was intial response to thalidomide and her lichen planus cleared after 15 months of treatment. However two further courses of thalidomide were ineffective for recurrence of lichen planus. She had a trial of tocilizumab and rituximab for inflammatory musculoskeletal symptoms. Tocilizumab was effective in normalizing the CRP but this was not associated with clinical improvement. Similarly Rituximab seemed to reduce the polyclonal increase of IgG to normal levels from a peak of 28.4 g/L, but again there was no improvement clinically. In addition to these therapies the patient also received multiple courses of oral steroids which had a modest effect. Intra-articular steroid injections have provided some symptomatic relief.

Our case describes the abnormal immunological findings that may be present in SLC29A3 spectrum disorders. This has rarely been explicitly reported despite the observation that autoimmune conditions such as haemolytic anaemia [3,4] and pancytopenia [5] may be associated with the syndrome. To date we could only find three other cases which characterized the immune system in affected patients. Melki et al reported a patient with a confirmed mutation in the *SLC29A3* gene and clinical features of H syndrome which became apparent in the first year of life [10]. He was found to have raised IgG and IgA levels. Notably, the patient had intermittent febrile episodes coinciding with raised inflammatory markers, a feature specific to the case. Severe systemic inflammation was also reported in a case of PHID. Here a 12 year old girl presented scleroderma-like changes, cardiomyopathy, hepatosplenomegaly, and raised erythrocyte sedimentation rate and CRP. Although she was found to have significantly elevated serum amyloid A, no systemic amyloid deposits were observed on a whole-body serum amyloid P scintigraphy scan [11]. More recently, Fujita et al. reported a male patient with characteristics of H syndrome in addition to Raynaud's phenomenon and retroperitoneal fibrosis [12]. He was found to have raised inflammatory markers. Notably, this patient had a novel mutation in the *SLC29A3* gene, suggesting that different mutations within the gene may lead to variant phenotypes. Most importantly these reports suggest that SLC29A3 spectrum disorder patients have abnormal immunological findings which may have gone un-investigated in previous case reports.

Various treatments having being trialled with patients with phenotypic characteristics of SLC29A3 spectrum disorders including methotrexate, 6- mercaptopurine and interferon alpha. At best these therapies had a modest benefit. Inevitably, the information gleaned from such case reports must be interpreted with caution, as the patients were not all genotyped. Ciclosporin and cyclophosphamide therapy however have been tested in a patient with a confirmed *SLC29A3* mutation; cyclophosphamide was reported to have had no effect, while ciclosporin apparently led to an improvement [13]. In Melki's case colchicine, anakinra, canakinumab and adalimumab were sequentially tested with no clinical response; non-steroidal anti-inflammatory drugs however did reduce the frequency of pyrexial episodes [10]. Similarly anakinra and anti-TNF blockade were also not effective in the patient with cardiomyopathy, hepatosplenomegaly and raised SAA [11]. In Fujita's patient prednisolone had some effect in treating skin lesions [12].

Our case adds to this current body of literature by highlighting that this condition seems to be associated with chronic inflammatory response, paraproteinaemia and a clinically diverse range of features. Most importantly immunomodulatory treatments, including biological agents targeting the pro-inflammatory cytokines, do not appear to have a significant effect on this condition. Considering that expression of ENT3 is not limited to the hematopoietic stem cells, and that the clinical phenotype is probably not entirely due to the inherent abnormalities of the immune system, it is questionable that more radical procedures, such as bone marrow transplant, would be successful for treatment of these disorders.

**Funding**

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**Conflict of Interest**

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Figure 1. Clinical features of SLC29A3 spectrum disorders.

Figure 2. (A) Haematoxylin Eosin stain x25 magnification: lymph node showing capsular fibrosis, reactive germinal centres and dilated sinuses filled with large histiocytes.
(B) Haematoxylin Eosin stain x 400 magnification: lymph node showing enlarged histiocytes (marked with ) containing central nuclei and abundant pale cytoplasm with lymphophagocytosis.

Figure 3. IgG (red), IgA (green) and IgM (black) levels in g/l. *IgG Kappa monoclonal band was detectable by serum electrophoresis, however the paraprotein levels were too low for quantification

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Figure 1

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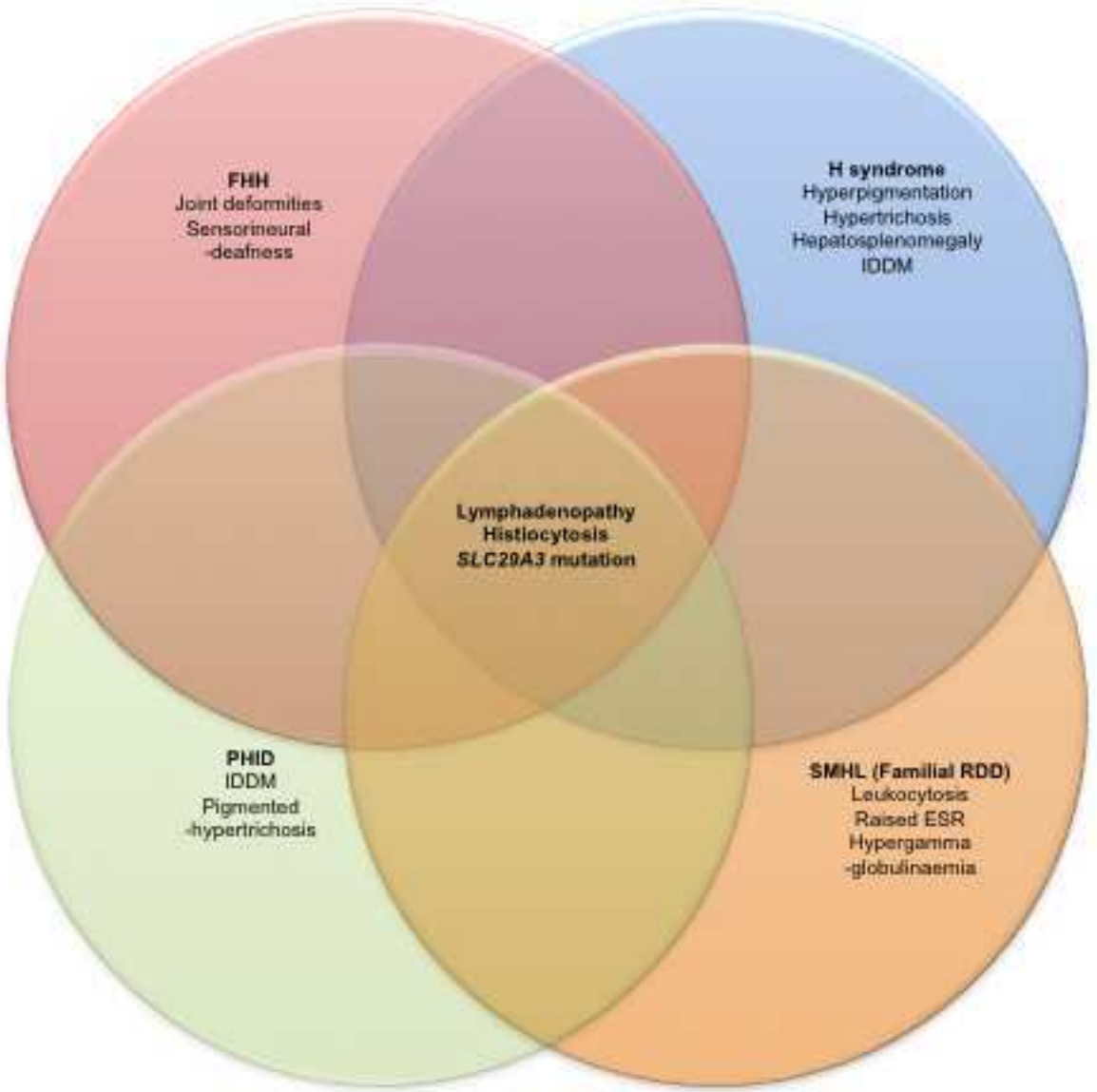

Figure 2

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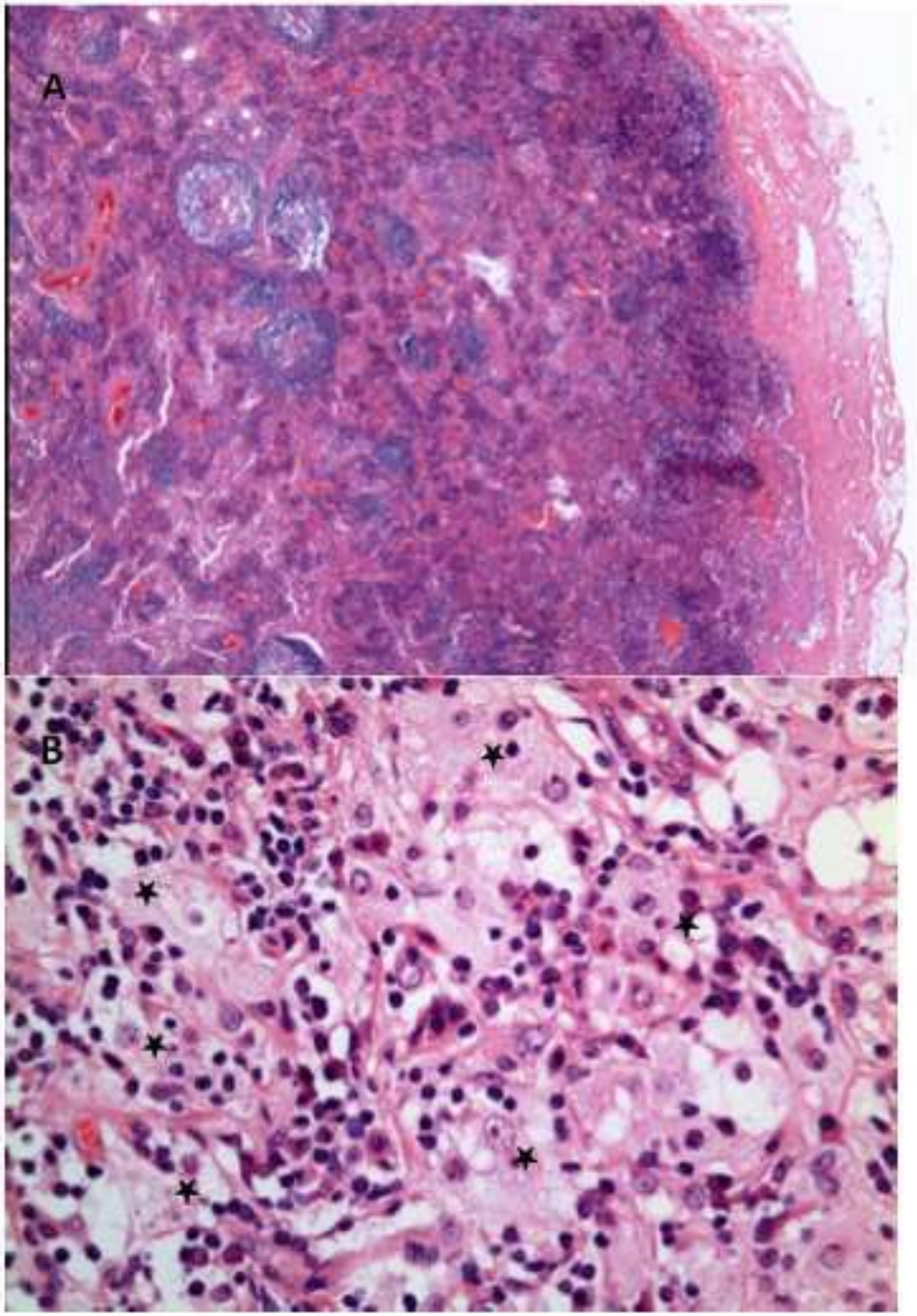

Figure 3

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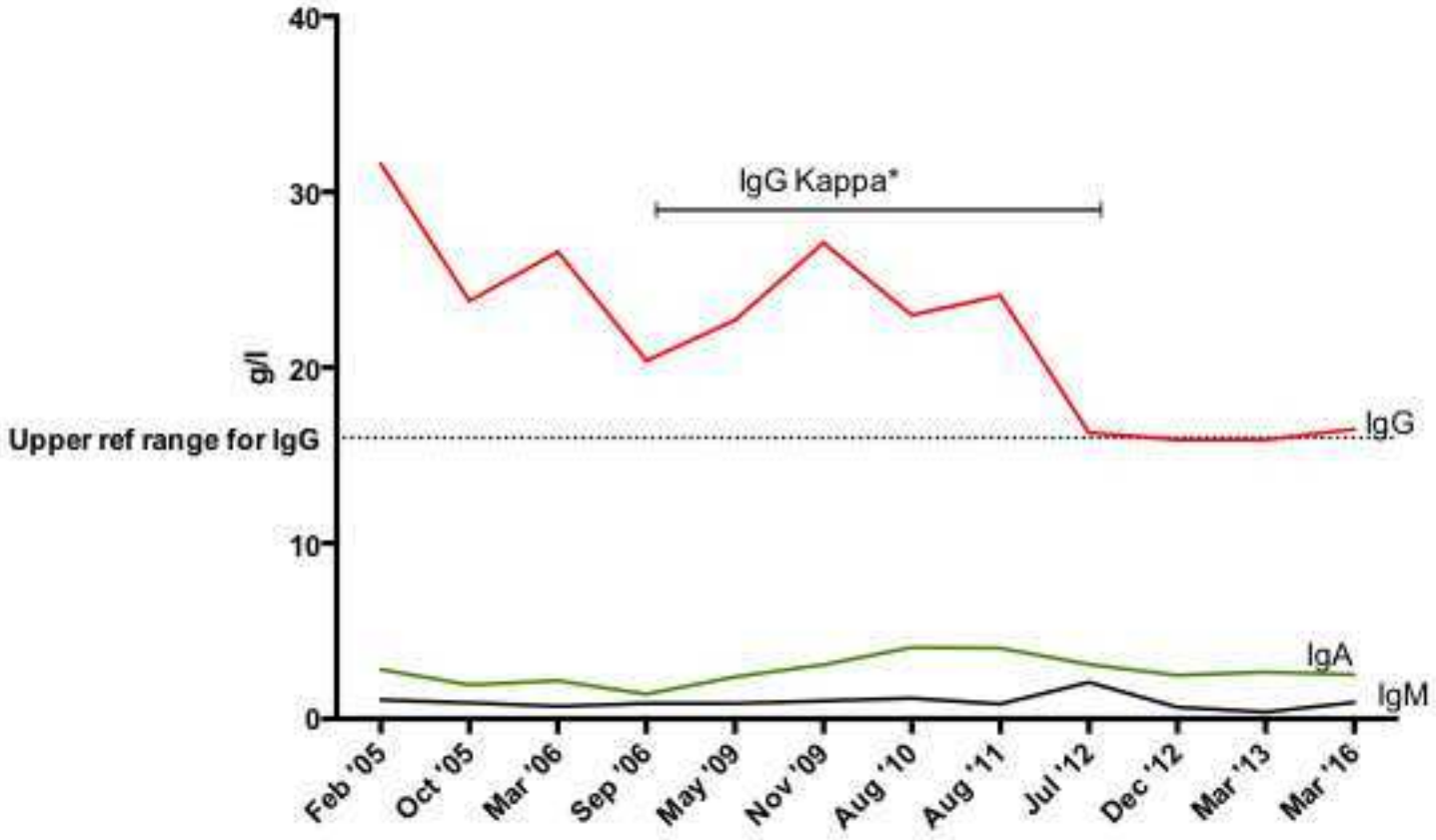

Table 1. Clinical features present in case patient

| Previously described in association with H syndrome | Features specific to this case |
|---|---|
| • Sensorineural deafness<br>• Interphalangeal joint deformities<br>• Pes Planus<br>• Short stature (0.4th centile)<br>• Arthralgia<br>• Myalgia<br>• Pancreatic insufficiency<br>• Malabsorption<br>• Diabetes Mellitus<br>• Skeletal abnormalities<br>• Hyperpigmentation<br>• Rosai-Dorfmann disease | • Proximal myopathy<br>• Anti-double stranded DNA positive<br>• Antinuclear antibody positive<br>• Lichen planus<br>• Alopecia totalis<br>• Lymphopenia |

**Table 2 Lymphocyte studies**

| Tests | 2006 | 2009 | 2010 | 2011 | Normal ranges |
|---|---|---|---|---|---|
| CD3+ Lymphocytes (cells/µl) | 302 | 484 | 411 | 501 | 700-2100 cells/µl |
| CD4+ T cells (cells/µl) | 201 | 370 | 305 | 400 | 300-1400 cells/µl |
| CD8+ T cells (cells/µl) | 73 | 106 | 94 | 95 | 200-900 cells/µl |
| NK cells CD56+ (cells/µ)l | 105 | 108 | 149 | 156 | 90-600 cells/µl |
| B cells (CD19+) cells/µl | 72 | 196 | 115 | 88 | 100-500 cells/µl |
| ratio | 2.75 | 3.49 | 3.24 | 4.21 | 1.07-1.87 |
| Marginal zone B cells CD19+ CD27+ IgD+ (% of CD19+) | | | 0.84% | | 0.5-8%* |
| Class switched memory B cells CD19+ CD27+ IgD- (% of CD19+) | | | 2.20% | | 3-18%* |
| PHA induced lymphocyte proliferation | | | Normal | | N/A |

PHA: phytohaemagglutinin;

* Schatorje EJ, et al. Age-matched reference values for B-lymphocyte subpopulations and CVID classifications in children. Scand J Immunol 2011;74:502-10

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Figure 1. Clinical features of SLC29A3 spectrum disorders.

Figure 2. (A) Haematoxylin Eosin stain x25 magnification: lymph node showing capsular fibrosis, reactive germinal centres and dilated sinuses filled with large histiocytes.
(B) Haematoxylin Eosin stain x 400 magnification: lymph node showing enlarged histiocytes (marked with ) containing central nuclei and abundant pale cytoplasm with lymphophagocytosis.

Figure 3. IgG (red), IgA (green) and IgM (black) levels in g/l. *IgG Kappa monoclonal band was detectable by serum electrophoresis, however the paraprotein levels were too low for quantification

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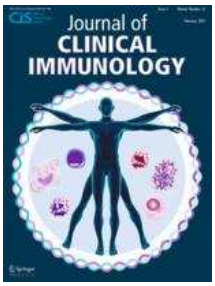


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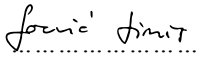
Signature  Date 24 Feb 2016

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