

# Proteus syndrome and immunodeficiency

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## Abstract

**A 10 year old boy with Proteus syndrome presented with a pericardial effusion of unknown aetiology. Immunological investigation revealed low serum IgG and IgA, accompanied by low levels of specific antibodies to pneumococcal and haemophilus type B polysaccharides. Circulating lymphocyte surface marker profile revealed T and B cell lymphopenia. This is the first report of hypogammaglobulinaemia occurring in the Proteus syndrome.**

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Proteus syndrome is a sporadically occurring hamartomatous syndrome first described in 1979<sup>1</sup> and subsequently named in 1983 by Wiedemann *et al.*<sup>2</sup> Proteus was the mythological god of the sea who had the ability to predict the future but disliked parting with information, and to avoid capture he would change his shape to disguise himself. It is now believed that Joseph Merrick (the Elephant Man) described in 1884 by Sir Frederick Treves had Proteus syndrome and not neurofibromatosis as previously thought.

Features of Proteus syndrome include: partial gigantism of hands and/or feet, hemihypertrophy, pigmented naevi, plantar hyperplasia ("moccasin" lesions), growth disorders, varicosities, macrocephaly, scoliosis, long bone overgrowth, cavernous haemangiomas, lipomas, and lymphangiomas.<sup>2,3</sup> Other features seen include cystic lung disease, cardiomyopathy, patchy dermal hypoplasia, and developmental delay in approximately 20% of cases.

To date immunodeficiency has not been reported in a patient with Proteus syndrome. We report on a 10 year old boy with Proteus syndrome, hypogammaglobulinaemia, and global lymphopenia.

## Clinical report

The patient is a 10 year old white boy born to non-consanguineous parents. He was born at term by emergency caesarean section because of failure to progress in the first stage. His mother was aged 24 and she was noted to have mild polyhydramnios during the pregnancy. His birth weight was 4.11 kg with Apgar scores of 7 at one minute and 9 at five minutes. On examination, he had periorbital oedema and enlargement of arms, right hand, right leg, and right foot. Initial blood investigations including chromosomes were normal. At age 1 year he had lymphoedema of his prepuce associated with a dribbling urinary stream and required circumcision. At age 7 a mass of his anterior

abdominal wall was surgically removed and later confirmed by histology to be a haemangioma. At age 8 he developed intermittent cough, breathlessness, and wheeze, resistant to bronchodilator treatment. A chest radiograph showed a large globular shaped heart and diffuse bilateral interstitial shadowing. A computed tomography scan of his chest confirmed the extensive nature of the interstitial shadowing and the changes were consistent with an interstitial pneumonitis. Cardiac ultrasound showed a large pericardial effusion which was drained under general anaesthetic; 400 ml of straw coloured fluid was removed which had an albumin concentration of 35 g/l and a white cell concentration of  $0.3 \times 10^9/l$ . Cytology and microbiological screen were normal. Viral serology was negative. He remained well for two months but his effusion reaccumulated and he required further surgical drainage. Pericardial biopsy at this time showed mild hypertrophy of mesothelial cells. To date he has remained symptom free and his effusion has not reaccumulated.

## Results

Serum immunoglobulins and IgG subclasses were measured by nephelometry. Lymphocyte surface marker analysis was performed by three colour flow cytometry. Specific antibodies to tetanus and diphtheria toxoids, and pneumococcal and haemophilus polysaccharides were measured by enzyme linked immunosorbent assay (ELISA). Immunological investigations revealed a low serum IgG and IgA (table 1). His IgG subclass profile showed reduced IgG1, IgG2, and IgG3 subclasses, accompanied by low concentrations of specific antibodies to pneumococcal and haemophilus type B polysaccharides. Specific antibodies to tetanus and diphtheria toxoids were normal. In order to assess the severity of the antibody deficiency,

Table 1 Serum immunoglobulins and lymphocyte markers

	Concentration
<i>Immunoglobulin (reference range) (g/l)</i>	
IgG (5.4-16.1)	2.80
IgA (0.5-2.4)	0.40
IgM (0.5-1.8)	0.50
IgG1 (3.6-7.3)	2.19
IgG2 (1.4-4.5)	0.43
IgG3 (0.3-1.1)	0.14
IgG4 (0.01-1.0)	0.11
<i>Lymphocyte (reference range) (<math>\times 10^9/l</math>)</i>	
Total lymphocyte count (2-2.7)	0.42
T cells	
Total CD3 +ve (1.4-2.0)	0.10
Total CD4 +ve (0.7-1.1)	0.05
Total CD8 +ve (0.6-0.9)	0.05
B cells	
CD19 +ve (0.3-0.5)	0.10
% of B cells expressing HLA-DR	100%
NK cells	
CD3 -ve, CD16 +ve (0.2-0.3)	0.17

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he was test immunised with 23 valent "Pneumovax" (pneumococcal vaccine) and conjugated Hib vaccine. Post-immunisation antibody concentrations were within normal limits. Circulating lymphocyte surface marker profile revealed T and B cell lymphopenia (table 1). Repeat serum immunoglobulins, IgG subclasses, and lymphocyte surface marker analysis at six and 12 months were unchanged from those at presentation. Investigation showed his purine pathway to be normal.

### Discussion

This is the first report of hypogammaglobulinaemia occurring in Proteus syndrome. While this association may be entirely coincidental, alternative explanations should also be considered. Hypogammaglobulinaemia and lymphopenia could be secondary to the loss of IgG and lymphocytes into lymphoedematous tissues, which can be a feature of this syndrome. The relatively normal serum IgM and IgA concentrations coupled with robust responses to test immunisation in the child reported would certainly accord with this hypothesis. An identical immunological profile is seen in intestinal lymphangiectasia, an unrelated disorder associated with IgG loss.<sup>4</sup> Definitive proof of IgG leakage as a cause of hypogammaglobulinaemia would require detailed imaging studies with radiolabelled IgG, a procedure that we considered to be clinically unjustifiable. Equally, we felt that invasive histological studies would contribute little to his management. It is also possible that the low IgG may reflect increased endogenous catabolism.<sup>5</sup> If the low IgG is caused by either leakage or increased catabolism, immunoglobulin replacement is likely to be of limited benefit.

In view of the combination of T cell lymphopenia and interstitial changes on chest radiography, he was commenced on prophylactic co-trimoxazole. Intravenous immunoglobulin replacement therapy was withheld in view of his robust responses to test immunisation and general well being. Interstitial pneumonitis has many different causes; the most worrying in this case would be opportunistic infection. However, we cannot rule out the possibility that the interstitial changes seen on chest radiography are secondary to lymphoedema. Despite having significant T cell lymphopenia and hypogammaglobulinaemia, he has no medical history of infections. His immunological profile has remained unchanged over the past 18 months and he has not had any further respiratory symptoms.

Although the nature of the association between hypogammaglobulinaemia and Proteus syndrome in this patient is speculative, we have reported it to alert clinicians to consider immunological investigations in the assessment of new patients with Proteus syndrome.

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