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Leukocyte Adhesion Deficiency Type 1 Due to Novel *ITGB2* Mutation

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Abstract

Aim
Marked neutrophilia and omphalitis in an infant resulted in the diagnosis of the first case of leukocyte adhesion deficiency type 1 (LAD1) in Ireland.

Diagnosis
LAD1 requires specific molecular diagnostics for its correct identification.

Results
Early identification of this disorder allowed for rapid referral for haemotopoeitic stem cell transplant which has resulted in an excellent outcome for this patient.

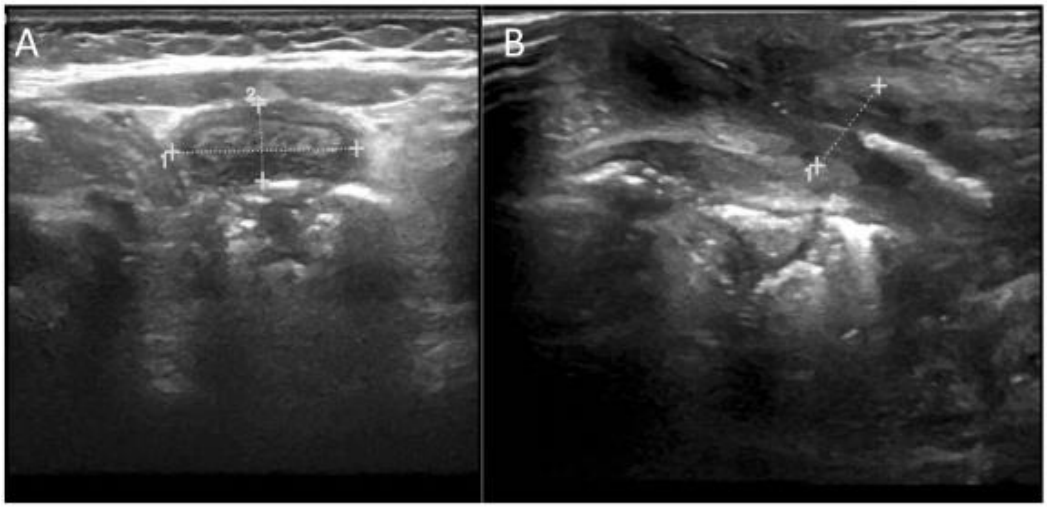
Conclusion
The identification of a previously unknown ITGB2 mutation resulting in LAD1 in Ireland should alert physicians to the diagnostic possibility of this extremely rare disorder.

Introduction

Leukocyte adhesion deficiency is a rare autosomal recessive disorder characterized by recurrent infections as a result of a defective homing response of neutrophils and macrophages. There are three subtypes, Leukocyte adhesion deficiency type 1 (LAD1) being the most common, with 334 cases reported to date[1].

Here, we present a novel *ITGB2* mutation resulting in a severe phenotype of LAD1, and the first reported case of LAD 1 in an Irish child. The patient is the second child to Irish parents. He presented at twenty-nine days of age with a respiratory tract infection and umbilical cellulitis was noted. He received Flucloxacillin intravenously for three days and was discharged on oral antibiotics thereafter. Notably, total white blood cell (TWBC) count was elevated at $52.6x10^9$/L, neutrophils $35.7x10^9$/L, lymphocytes $14.7x10^9$/L and C-reactive protein (CRP) 69.3mg/L (NR<5mg/L). Three weeks later he re-presented with ongoing periumbilical cellulitis and serous discharge. Repeat testing revealed TWBC of $61.5x10^9$/L with neutrophilia ($39.0x10^9$/L), and a CRP of 142mg/L. Abdominal ultrasound identified a 3.5cm long tract extending from the umbilical surface to subcutaneous umbilical tissues (Fig.1A). Surgical exploration revealed a superficial collection which grew pan-susceptible *E. coli*. Postoperative ultrasound showed a tubular structure, resembling an inflamed urachal remnant (Fig.1B).

Figure 1: Collection (dimensions 1x2x1cm) prior to incision and drainage (A); appearance of abdominal wall structures following surgical intervention (B). Note the tubular appearance of deep deated omphalitis extending beyond the abdominal wall structures.



Immunological evaluation was commenced and antibiotic cover was broadened to include piperacillin/tazobactam and fluconazole. Targeted history revealed delayed umbilical cord detachment at 21days of age. CD18 expression on leukocytes was less than 1% (<19 units) of expected, consistent with a diagnosis of a severe phenotype of LAD1. Following further investigation at the Immunology Laboratory at Great Ormond Street Children's Hospital London, he was found to be homozygous for a novel missense mutation in *ITGB2* (c.1034T>C)[5].

The patient completed a course of antibiotics resulting in resolution of the omphalitis and was subsequently commenced on co-trimoxazole and fluconazole prophylaxis before undergoing a fully matched, maternal peripheral blood stem cell transplant at age four and a half months. He had an uncomplicated transplant course, with neutrophil engraftment by day +18, and displays 100% donor chimerism at nine months post-transplant with no graft-versus-host disease.

Discussion

The primary defect in LAD1 lies in expression and function of the Integrin2 subunit-β, or CD18 antigen, which is encoded by *ITGB2* (21q22.3)[1;2] and belongs to the integrin family.

Four integrin-α subunits associate with CD18 to form heterodimers, LFA-1 (CD11a18), Mac-1/CR3 (CD11b18), alphadbeta2 (CD11d18) and p150,95 (CD11c18); expressed on neutrophils, lymphocytes, macrophages, and NK-cells. They are essential for adhesion to antigen-presenting and endothelial cells. Reduced or absent CD18 expression results in impaired homing of immune cells and their ability to extravasate[3]. Clinical presentation of LAD1 depends on the level of CD18 expression and residual function[3]. Patients with severe phenotype present in infancy with delayed umbilical cord separation and life-threatening infections characterized by excessive neutrophilia and lack of pus formation due to the inability of neutrophils to home to infection site, leave the blood stream and attend to tissue injury. The abdominal findings were interpreted in the context of an immune defect once the diagnosis had been established. Similar presentations should caution clinicians to consider LAD1 in neonates with omphalitis and neutrophilia[1].

To date, 323 cases of LAD 1 have been reported worldwide with a mutation identified in only 43% of patients[4]. There are currently 96 identified pathogenic mutations[1]. Our patient was homozygous for a novel, intronic single nucleotide substitution in position c.1034T>C, disease-causing by virtue of resulting in a missense variant and absent Integrin-β2 expression.

Without timely haematopoietic stem cell transplantion (HSCT), LAD1-associated mortality is substantial. However, for the 101 patients having undergone HSCT since 1993, event-free survival rate at 94 months was over 90%[4].

Both parents and the sister are heterozygous for the same mutation. All are healthy and asymptomatic. The parents have remote common ancestors on an island off the coast of the Irish Southwest, which may also serve as explanation for the maternal graft being a full match. The area was severely affected by the Great Irish Famine, as a result of which 1.5 million people emigrated, the vast majority to the United States. It would be of interest to pursue family ancestry should the same mutation be identified in a patient overseas. With our ever-expanding knowledge of genetics in rare conditions such as LAD1, reporting of ethnicity and ancestry in new cases may also allow for targeted genetic re-analysis in those for whom a mutation has not previously been identified.

This case serves as a reminder that frontline clinicians must retain a high index of suspicion for primary immune defects, as early identification and rapid intervention are critical in order to optimize patient outcomes.

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Declaration of Conflicts of Interest:
The authors declare no conflict of interest.

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