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ASTUTE CLINICIAN REPORT

A Novel Treatment in X-Linked Agammaglobulinaemia - Hyperbaric Oxygen Therapy in Refractory Chronic Wounds

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Abstract Chronic wounds are a rare complication of X-linked agammaglobulinaemia (XLA). Fastidious organisms such as helicobacter bills have been reported in XLA with chronic wounds but sterile chronic wounds also occur. Hyperbaric Oxygen Therapy has been used in chronic wounds but has not previously been reported in primary antibody deficiencies. We present a case of a chronic wound in a patient with XLA refractory to antimicrobial therapy that made a remarkable recovery following Hyperbaric Oxygen Therapy.

Keywords X-linked agammaglobulinaemia · hyperbaric oxygen therapy · chronic wound

Introduction

X-linked agammaglobulinaemia (XLA) is a primary immunodeficiency characterised by B cell cytopenia and panhypogammaglobulinaemia caused by mutations in the Bruton's tyrosine kinase gene. Recurrent infections with encapsulated bacteria, enteroviruses and parasites are observed. Skin and wound infections are uncommon but chronic wound infection with *Campylobacter*, *Helicobacter bilis* [1, 2] and "*flexispira*" like organisms [3] is described. Chronic non-infectious wounds are rare [4].

Chronic wounds are defined as having failed to achieve anatomical and functional integrity over a timely period [5]. Failure of healing may be attributed to corticosteroids, persistent infection, tissue hypoxia, unrelieved pressure, obesity, diabetes mellitus and squamous cell carcinoma [6]. Chronic wounds may cause functional, aesthetic and psychological impairment.

Hyperbaric oxygen therapy (HBOT) has been used successfully in the treatment of chronic wounds. The basis for its efficacy is partially understood, involving improved neovascularisation, reduced production of pro-inflammatory cytokines and increased synthesis of growth factors and collagen [7]. A Cochrane review in 2012 looked at HBOT for chronic wounds and concluded that there was a statistically significant benefit at 6 weeks in ulcer healing, but this was not evident at longer term follow-up and there was no statistically significant reduction in major amputation. Trials suitable for inclusion in this review were mainly in regard to diabetic foot ulcers [8]. A 4 years old patient with Chronic Granulomatous Disease (CGD) and refractory osteomyelitis of the mandible made a recovery following HBOT [9] but no reports of HBOT in XLA have been published. This case describes resolution of chronic, severe distal limb ulceration with HBOT in a middle-aged male with XLA.

Case Description

The patient was presumed to have XLA at 6 months of age, presenting with recurrent respiratory tract infections and viral gastroenteritis. Investigations revealed panhypogammaglobulinaemia. There was a family history of XLA. $CD19^+$ B lymphocytes were undetectable when immunophenotyping became available. At age 36, minor blunt trauma to the right leg followed a simple fall onto rubble. There was no underlying haematoma. The skin was not broken but over the next 48 h the leg became erythematous, painful and was accompanied by fever, neutrophilia (9.39×10^9 cells/litre, normal range 2.0–7.5) and elevated CRP (86 mg/L, normal range 0–5). A well-

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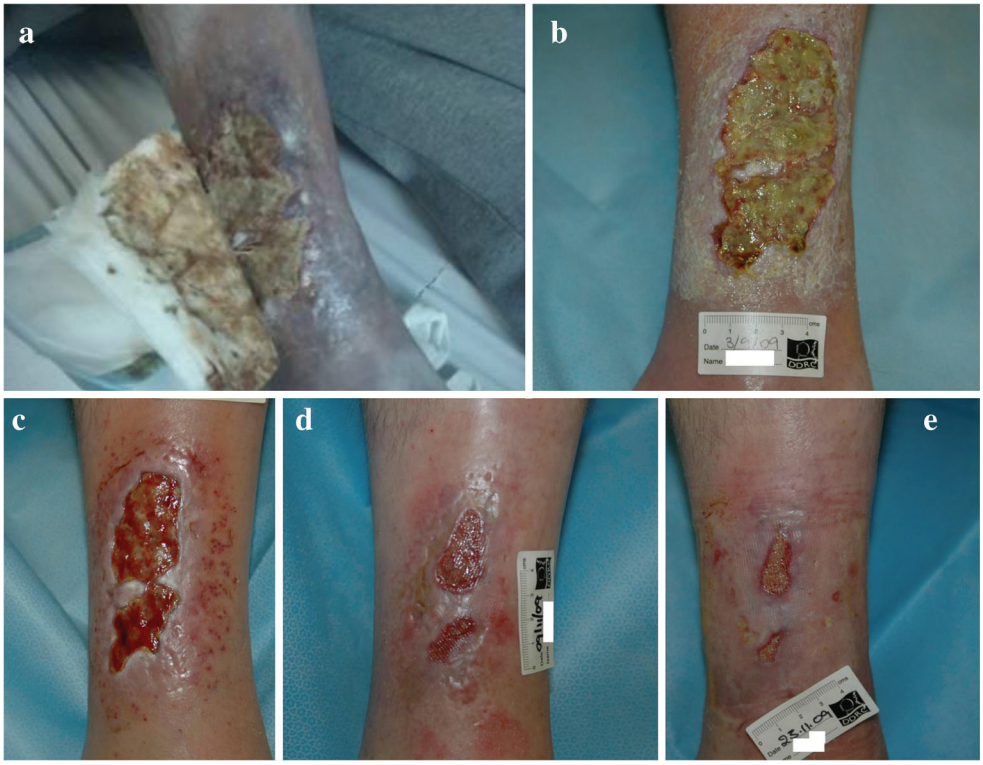

Fig. 1 **a** before HBOT **b** Day 3 HBOT **c** Day 23 HBOT **d** Day 50 HBOT **e** Day 64 HBOT

demarcated 50×25 mm area of inflamed skin was present. A diagnosis of cellulitis was made and there was a good initial response to oral flucloxacillin. However, the cellulitis rapidly returned (within 1 week) after treatment. Despite 3 further courses of oral antibiotics, the cellulitis worsened. The area increased to 220x55mm, CRP to 222 mg/L and neutrophils to 13.55×10^9 cells/litre. This prompted a 21 days hospital admission for intravenous Meropenem. There was partial resolution before re-emergence of cellulitis within 1–2 weeks of completion of treatment and subsequently this progressed to ulceration at 12 months. Magnetic resonance imaging and isotope bone scanning did not reveal bony involvement. Multiple hospital admissions over the following 3 years were required for recurrent episodes of cellulitis. Wound dressing and therapy with various multiple combinations of Ciprofloxacin, Clindamycin, Meropenem, Gentamicin, Imipenem, Amikacin, Minocycline, Vancomycin, Tazocin, Fucidic acid, Clarithromycin and Linezolid resulted in transient improvement. However, typically once antibiotics were completed the affected area would break down again. Wound and blood cultures were repeatedly sterile. There was no evidence of arterial insufficiency or venous disease and there was no history of diabetes mellitus. Tissue biopsy at the edge of the wound demonstrated marked fibrosis within the dermis with proliferation of fibrohistiocytic cells and a background of inflammatory cells. There was extension of fibrosis and sclerosis into the subcutaneous fat but insufficient tissue to make a definitive diagnosis of lipodermatosclerosis. Ziehl-Neelsen and Periodic Acid Schiff staining was negative. 16S ribosomal (r)DNA PCR analysis performed retrospectively on paraffin-embedded biopsy specimens did not identify *campylobacter*, *helicobacter* or *flexispira* species. The patient was reviewed by plastic and vascular surgeons, tissue viability and infectious disease services. No definitive reason for persistence of the chronic wound was identified and because of a fear of causing further damage, neither surgical debridement nor skin grafting was undertaken. The wound continued to worsen and severe pain prompted the patient to request amputation. At

Table 1 Laboratory results prior to and following HBOT

Results	At time of up-titration of IVIg	Immediately before commencing HBOT	7 weeks after commencing HBOT	20 weeks after commencing HBOT
CRP (mg/L)	78	203	3	4
HB (g/dL)	104	106		139
WCC ($\times10^9$/litre)	14.9	5.8		8.6
Trough IgG (g/L)	7.50	14.50	10.10	13.60

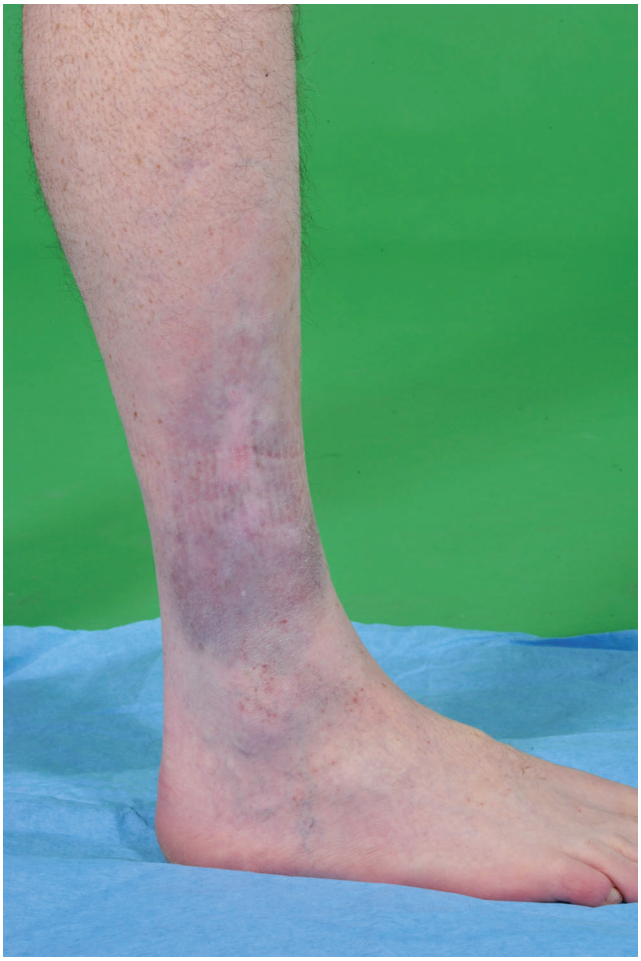

Fig. 2 Appearance of leg 5 years after completion of HBOT

this stage the intravenous immunoglobulin dose was increased from 640 mg/kg/month (minimum IgG trough level 7.5 g/L) to 820 mg/kg/month but no benefit occurred over a 4 months period. The patient thereafter commenced HBOT. Over the course of 3 months, 50 treatment sessions were performed with the patient receiving HBOT at 2.2 atmospheres absolute for 90 min per session. Benefit was seen immediately with almost complete recovery of epithelial integrity and improvement in tissue inflammation without further necessity for antimicrobials [Fig. 1]. Substantive improvement in inflammatory markers [Table 1], pain severity and improved quality of life was observed. No further HBOT has been required for the past 5 years; the skin remains intact [Fig. 2].

Discussion

Normal wound healing takes place in three overlapping phases; inflammation, proliferation and remodelling [10]. The inflammatory phase includes haemostasis and the release of chemokines and growth factors stimulating neutrophil and monocyte migration into the tissue. During the proliferative phase, re-epithelialisation, fibroplasia and angiogenesis predominate. The remodelling phase consists of the deposition and alteration of the collagen matrix. Delayed healing of wounds is typified by a disordered progression through these stages. Failure of keratinocytes to respond to chemoattractant signals has been observed, as has the impaired response of fibroblasts to TGF-β and other growth factors [10].

XLA may have proven a risk factor for the development of a chronic wound in this patient. While not detected in this patient *flexispira*, *Campylobacter* or *Helicobacter bilis* infection could have presented in this manner and these organisms should be looked for, requiring access to 16 s rRNA gene sequencing. The retrospective testing of paraffin embedded biopsy specimens in this sample may have proven inferior to fresh, unmanipulated skin. Additionally, wound biofilms could prove more resistant to treatment in XLA than immunocompetent individuals. Biofilms are bacterial aggregates capable of forming a barrier to phagocyte attachment and penetration. Sequestration of antibodies and complement within the biofilm reduces the effectiveness of the immune response and antimicrobial therapy becomes ineffective failing to generate the necessary minimum inhibitory concentration for organisms within the biofilm [11].

The role of oxygen in chronic wounds is complex. Hypoxic conditions in the early phase of wound healing provide a stimulus for healing but chronic hypoxia frustrates overall repair [6]. Both hypoxic and hyperoxic conditions appear to be drivers for macrophage production of vascular endothelial growth factor (VEGF) [12] while oxidant species produced by phagocytes serve to promote healing but in excess antagonise this process. HBOT increases the oxygen availability to chronic wounds which, due to defective angiogenesis, will have chronic tissue hypoxia. The amount of oxygen dissolved in plasma increases under HBOT conditions to supranormal levels [6]. The success of HBOT in this case may be attributable to (i) a reduction in circulating proinflammatory cytokines, (ii) the promotion of angiogenesis and (iii) increased synthesis of growth factors and collagen. This case highlights the role of HBOT in chronic wounds and its suitability in patients with primary immunodeficiencies. We conclude that HBOT is a beneficial treatment modality in the management of refractory chronic wounds in XLA.

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