Thalassaemia intermedia: the role of erythroexchange in the treatment of an indolent wound

Marco Pignatti[1], Maurizio Govoni[2], Giuseppe Graldi[2], Lucrezia Pacchioni[1], Giorgio De Santis[1], Caterina Borgna[3]

[1]Department of Plastic and Reconstructive Surgery, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena; [2]Blood Transfusion Service, Ferrara; [3]Department of Medical Sciences/Paediatrics, University of Ferrara, Ferrara, Italy

Introduction

Thalassaemia intermedia is a haemoglobinopathy in which, by definition, the patient maintains satisfactory levels of haemoglobin without needing transfusions. Indeed, the condition is also called non-transfusion-dependent thalassaemia. Nevertheless, at some time during the patient's lifetime, transfusion therapy may become necessary to guarantee a level of haemoglobin adequate for the activities of normal life. Thalassaemia intermedia is most commonly associated with a homozygous or compound heterozygous state for two beta-thalassaemia alleles but the severity of the clinical picture is related to the patient's genotype and the consequent degree of globin chain imbalance[1]. The level of foetal haemoglobin (HbF) is usually variably elevated. In addition, patients with thalassaemia intermedia can suffer from an atypical form of pseudoxanthoma elasticum (PXE), a multisystem disorder affecting, among others, the elastic tissues of the arteries and leading to degeneration and calcification of the elastic lamina of the arterial wall[2].

At the level of the ankle, low haemoglobin concentrations associated with abnormal red cell rheology and increased haemoglobin F cause tissue hypoxia that promotes thinning of the skin and subcutaneous fragility. As a consequence, trophic ulcers are a common finding in adult patients[3]. We report here the difficult healing of a surgical wound in a patient with thalassaemia intermedia and the beneficial effect obtained with erythroexchange that, decreasing the level of HbF in favour of HbA, improved the oxygen availability in the area and promoted healing.

Case report

The patient, a 62-year old male, affected by thalassemia intermedia secondary to the complex mutation $-\alpha/\alpha\alpha$ β-87 C→G39/β IVSI nt1 and by acquired PXE, underwent orthopaedic surgery for arthrosis of the ankle with positioning of a prosthesis. The

Figure 1 - Appearance of the wound at different times.
a) The surgical wound as it appeared at first referral, 2 months after orthopaedic surgery. Exposed tendons are visible. b). Healthy granulation tissue was obtained on most of the wound surface after multiple debridement and negative pressure dressing changes. c) Granulation tissue growing over the exposed tendons a few days after erythrocytopheresis and increasing rapidly. d) Complete healing on day 172 (69 days after the first apheresis) after re-epithelisation of the healthy granulation tissue from the surroundings.

*Blood Transfus 2014; **12**: 124-6* DOI 10.2450/2013.0181-13

procedure was apparently successful but, 2 months later, the surgical wound was still open, no granulation was visible and two tendons were exposed (Figure 1a and b). The patient started hyperbaric oxygen therapy, which was continued for a total of 20 sessions without improvement.

He was at that point referred to the Division of Plastic Surgery of the University of Modena, where debridement of the necrotic tissue was performed and negative pressure therapy (VAC; KCI UK Holdings Ltd, Wimborne, Dorset, United Kingdom), was applied. VAC dressing changes and debridement of the non-viable tendon fibres were performed twice a week until healthy granulation tissue was obtained on most of the wound surface (Figure 1c).

Since the tendons were still exposed, the option of covering the defect with a flap was considered. Given the patient's medical condition and the fact that the quality of the soft tissues in the leg and foot was not suitable, a pedicled flap was considered not feasible, while a free flap, taken from another part of the body and requiring microsurgical vessel anastomosis was excluded because of diffuse calcification of all the arterial vessels, and in particular of the tibial arteries shown by plain X-ray (Figure 2) and by angiographic computed tomography scanning. A more conservative surgical approach was, therefore, chosen to cover the exposed tendons, applying an acellular dermal matrix, Integra (Integra Life Sciences, Plainsboro, NJ, USA) to the wound[4]. After 21 days, as suggested by the producers, the upper silicone layer was removed and a split thickness skin graft was applied over the Integra. Despite these treatments, complete healing was still not obtained 3 weeks after skin grafting and 8 weeks after referral.

Figure 2 - X-ray showing diffuse calcification of the tibial artery.

Laboratory tests showed a haemoglobin concentration of 10.2 g/dL, white blood cell (WBC) count of 12.97×10^9/L and serum ferritin of 1,244 ng/mL. High performance liquid chromatography of the haemoglobin showed HbF 70% and HbA_2 3.8 %.

On day 105 after orthopaedic surgery, erythroexchange was proposed, with the aim of decreasing the level of foetal haemoglobin and thereby increasing the release of oxygen to the tissues, without increasing total haemoglobin.

The treatment was carried out with a continuous flow blood cell separator (COM.TEC Fresenius Kabi, Bad Homburg, Germany) with one red blood cell volume (1,450 mL) exchanged each time[5]. The haemoglobin level was kept at 10.7 g/dL, while the HbF dropped to 35%, with a corresponding increase in HbA. The nucleated red blood cell (NRBC) count was 36,700/ mm^3 before the first erythroexchange and decreased to 25,423/ mm^3 at the end of it. After 3 days the exposed tendons started granulating.

The erythrocyte exchange was repeated after 1 month: the proportion of HbF decreased from 41% to 21%, and the NRBC count decreased from 36,200/mm^3 to 18,255/mm^3. Thereafter, re-epithelisation of the wound from the surroundings was rapid and on day 172 (69 from the first apheresis) healing was complete (Figure 1d).

Discussion

Wound healing has been described as a carefully-scripted drama[6]. After an injury, multiple biological pathways immediately become activated and are synchronised to respond under the control of numerous cytokines. However, this delicate balance between cells and mediators can be disrupted and the closure of the wound can be delayed. In the case of our patient the cause of delayed wound healing was multifactorial, being secondary to arterial insufficiency, microangiopathy and hypoxia.

In thalassaemia intermedia, haemolysis-induced low arginine and nitric oxide bioavailability, associated with oxidative stress and hypercoagulability have been demonstrated. These factors together with anaemia and iron overload contribute to endothelial dysfunction and development of vasculopathy[7]. The additional presence of PXE, whose pathophysiology is attributed to iron-induced oxidative tissue damage[2], decreases adequate circulation in the extremities. In our patient the wound produced by orthopaedic surgery had become indolent and did not respond satisfactorily to conservative treatment. All the scientifically-sound

surgical techniques available[8,9] had limited success in this patient. A key factor to achieve normal wound healing is to optimise the oxygen concentration in or around the wound in order to stimulate fibroblast proliferation and differentiation, to increase collagen formation and cross-linking, to augment neovascularisation and to stimulate leucocyte microbial killing. Resistance to infection is dependent on local oxygen tension because the main mechanism by which polymorphonuclear leucocytes kill bacteria uses oxygen[10].

Erythroexchange is commonly used in patients with sickle cell anaemia, in whom HbS is substituted with HbA, preventing the typical non-covalent polymerisation that occludes vessels, thereby blocking or slowing blood flow[11]. We are aware of only one case in which exchange transfusions were used successfully for the treatment of persistent leg ulcerations[12]. Improving the delivery of oxygen to the tissues by decreasing the oxygen affinity of haemoglobin may improve tissue oxygenation. The oxygen dissociation curve of HbF is shifted to the left relative to the curve of HbA because arterial oxygen pressures in the foetus are low, and the uptake from the placenta and release of oxygen to the developing tissues need to be enhanced.

Hyperbaric oxygen therapy, which has been demonstrated to be of some utility in diabetic ulcers[13] in the presence of HbF did not produce much effect in our patient. Conversely, the increase in oxygen availability brought about by the exchange of red cells containing HbA instead of HbF rapidly improved healing. Simple top up transfusions were not considered appropriate because the thrombotic risk, always present in thalassaemia intermedia[7], was aggravated in our case by PXE in a patient with a relatively high haemoglobin level and a large number of NRBC. As expected, the NRBC count was reduced by approximately 50% with each erythroexchange. In addition exchange transfusion was felt to be able to guarantee a faster reduction of HbF, at the same time avoiding volume and iron overload. Finally, the risk of infection associated with platelet-derived healing factor[14], albeit small, was considered excessive in the presence of a prosthesis.

In conclusion we suggest that erythroexchange should be considered in patients with thalassaemia intermedia with high levels of HbF, whenever healing of lesions in the extremities, whether spontaneous or from trauma of any origin, is slow and unsatisfactory.

Keywords: thalassaemia, wound, eythroexchange, erythrocytoapheresis, exchange blood transfusion.

The Authors declare no conflicts of interest.

References

1) Galanello R. Recent advances in the molecular understanding of non-transfusion-dependent thalassemia. Blood Rev 2012; **26**: S7-11.
2) Fabbri E, Forni GL, Guerrini G, Borgna-Pignatti C. Pseudoxanthoma-elasticum-like syndrome and thalassemia: an update. Dermatol Online J 2009; **15**: 7.
3) Borgna-Pignatti C., Marsella M, Zanforlin N. The natural history of thalassemia intermedia. Ann N Y Acad Sci 2010; **1202**: 214-20.
4) Menn ZK, Lee E, Klebuc MJ. Acellular dermal matrix and negative pressure wound therapy: a tissue-engineered alternative to free tissue transfer in the compromised host. J Reconstr Microsurg 2012; **28**: 139-44.
5) Masera N, Tavecchia L, Pozzi L, et al. Periodic erythroexchange is an effective strategy for high risk paediatric patients with sickle-cell disease. Transfus Apher Sci 2007; **37**: 241-7.
6) Krafts KP. Tissue repair: the hidden drama. Organogenesis 2010; **6**: 225-33.
7) Cappellini MD, Musallam KM, Poggiali E, Taher AT. Hypercoagulability in non-transfusion-dependent thalassemia. Blood Rev 2012; **26** (Suppl 1): S20-3.
8) Iorio ML, Shuck J, Attinger CE. Wound healing in the upper and lower extremities: a systematic review on the use of acellular dermal matrices. Plast Reconstr Surg 2012; **130** (5 Suppl 2): 232S-41S.
9) Argenta LC, Morykwas MJ, Marks MW, DeFranzo AJ, Vacuum-assisted closure: state of clinic art. Plast Reconstr Surg 2006; **117** (7 Suppl): 127S-42S.
10) Niinikoski JH. Clinical hyperbaric oxygen therapy, wound perfusion, and transcutaneous oximetry. World J Surg 2004; **28**: 307-11.
11) Danielson CF. The role of red blood cell exchange transfusion in the treatment and prevention of complications of sickle cell disease. Ther Apher 2002; **6**: 24-31.
12) Aessopos A, Kati M, Tsironi M, et al. Exchange blood transfusions for the treatment of leg ulcerations in thalassemia intermedia. Haematologica 2006; **91** (5 Suppl): ECR11.
13) Kranke P, Bennett MH, Martyn-St James M, et al. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev 2012; **4**: CD004123.
14) Josifova D, Gatt G, Aquilina A, et al. Treatment of leg ulcers with platelet-derived wound healing factor (PDWHFS) in a patient with beta thalassaemia intermedia. Br J Haematol 2011; **112**: 527-9.

Arrived: 20 June 2013 - Revision accepted: 30 September 2013
Correspondence: Caterina Borgna
Clinica Pediatrica Università di Ferrara
Via Aldo Moro 8
44123 Cona (FE), Italy
e-mail: c.borgna@unife.it