Clinics in Surgery

Case Report
Published: 17 Jun, 2019

Negative Pressure Wound Therapy with Potential Autologous Stem Cell Therapy: The Challenge and Future of Complex Defect Healing?

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Abstract

The complex wound defect always needs a long-term clinical intervention and flap coverage, because of massive soft tissue loss with continuous sepsis and poorest granulation tissue with the impair healing process. Here, we report a 22-year-old male had suffered a work-related High Voltage Electrical Burn (HVEB), result in extensive deep tissue damage (about 12% visible total body surface area burns with a 3rd to 4th degree) with abdominal wall complex defect. A series of surgical operations and medical care's had taken by the traumatic team, including Negative Pressure Wound Therapy (NPWT) with an autologous stem cell therapy, e.g., isolated from the iliac bone marrow aspirate and injection. Our results suggested that the NPWT with stem cell treatment is successful, the complex wound defect is covered in observation time and wound healing is satisfactory.

Keywords: Multiple trauma; High-voltage electrical burn; Complex wound defect; Negative pressure wound therapy; Bone marrow aspirate; Stem cell therapy

Introduction

Wound healing is considered as a coordinated process involving complex mechanisms that proceed in various stages which include blood clotting, inflammation, cellular proliferation, angiogenesis and remodeling of the extracellular matrix. During the past decades, the management of wound healing has evolved rapidly; Negative Pressure Wound Therapy (NPWT) has become one of the standard treatments to clinic patients with various acute and chronic wounds who require non-invasion intervention [1]. In recent years, stem cell therapy is highly recommended a trend on wound healing and is becoming one of the useful therapeutic methods in clinic [2].

As an intractable challenge for surgeon and patient, the complex defect would always is famous of massive soft tissue loss with continuous sepsis and poorest granulation tissue with impair healing, which need a long-term clinical invention and heavy financial burden. Majority of complex defect wound underwent various flap grafts and patient have to suffer a new round of full function loss by the reconstruction surgery. The recent development of advanced wound healing technology has triggered the use of cell therapy to improve wound healing conditions [3]. One of the strategies is to identify and enrich with functionally superior stem cell subsets, such as bone marrow extractive and culture; another approach is to optimize the stem cell delivery to the harsh wound, such as bone marrow aspirate and injection [4]. However, the concept of both ideas for using stem cells in tissue regeneration is limited by the source of autologous stem cell numbers. Thus, the inducible Pluripotent Stem Cells (iPSCs) made from autologous donor cells and can supply unlimited source stem cells which have become a basic concept of regenerative medicine, is still awaiting identification that can be safely and efficiently used in the clinic. Occasionally, we underwent a traditional NPWT combines with stem cell therapy will be a more efficient effect on complex defect wound healing. We will discuss the benefits of the combination therapy and their mechanism potential.

Case and Treatments

A 22-year-old previously healthy male had suffered a work-related HVEB, result in extensive deep tissue damage to the left upper limb and hypogastrium with abdominal wall complex

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Received Date: *08 May 2019*
Accepted Date: *14 Jun 2019*
Published Date: *17 Jun 2019*

Citation:
Yang F, Bai X, Xie J, Chen J, Dai X, Li Y, et al. Negative Pressure Wound Therapy with Potential Autologous Stem Cell Therapy: The Challenge and Future of Complex Defect Healing?. Clin Surg. 2019; 4: 2481.

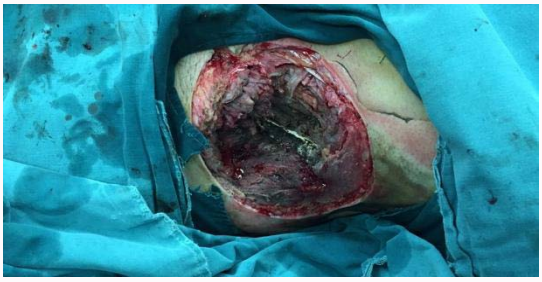


Figure 1: The patient immediately after admission, showing extensive deep tissue damage to left upper limb and hypogastrium with abdominal wall complex defect (about 10% visible total body surface area burns with 3rd degree).

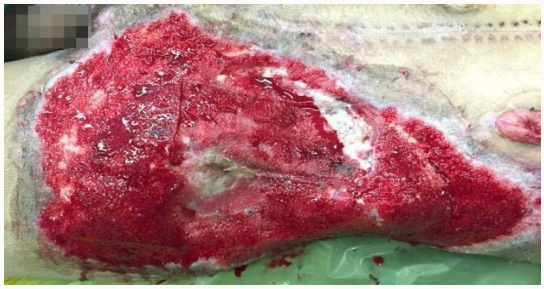


Figure 2: A series of surgical operations and medical care's had taken by the traumatic team, including emergency debridement, fasciotomy, laparotomy with colectomy and colostomy on Day of Admission (DOA).

defect (about 12% visible total body surface area burns with a 3rd to 4th degree) (Figure 1), was admitted timely. A series of surgical operations and medical care's had taken by the traumatic team, including emergency debridement, fasciotomy, laparotomy with colectomy and colostomy on the Day of Admission (DOA) (Figure 2). Postoperatively, the patient continued to receive appropriate antibiotics and blood transfusions as required. Nutritional support in the form of amino acid infusions and oral intake of high-protein and high-calorie feeds was instituted. After performing a consecutive wound observation and complete status assessment, axilla amputation and iliac osteotomy with NPWT had performed on 3rd DOA (Figure 3 & 4). Potential stem cell therapy of autologous iliac bone marrow aspirate (2 ml to 3 ml per time from left ilium) and injection (0.5 ml to 1 ml per site at the poor granulation tissues of defect) had performed during operations for total 6 times, on 10th, 15th, 19th, 24th, 29th, 36th DOA individually (Figures 5-10). On the 42nd DOA, coverage of the left hypogastric wound was performed using mesh skin autografts on the fresh granulation tissues successfully (Figure 11 & 12) and wound healing satisfactorily (Figure 13). The patient was discharged 18 days after grafting in the traumatic department and was referred to the rehabilitation department for advanced rehabilitative treatment. No other complications during the whole inpatient treatment period.

In summary, the patient remained in the hospital for a total of 60 days, 7 days of which were spent in the ICU. He was taken to the operating room a tot al of 6 times potential stem cell therapy by autologous iliac bone marrow aspirate and injection at the poor granulation tissues, and the complex wound defect was amazing healed stringendo without flap coverage.

Discussion

Multiple trauma and HVEB

High energy injury is one of the most important etiologic factors in multiple traumatic populations and leads to irreversible damage to different tissue types as the nightmare of medical care. Unfortunately, as the lowest resistance to High Voltage Electrical Burn (HVEB), high susceptibility to vessels and muscles makes them more vulnerable to thrombosis and a sequence of muscle necrosis. The necrosis results in extensive deep tissue injury and complex defects with potentially fatal outcomes, which is one of the most challenging problems in wound healing and regenerative medicine.

In cases with HVEB, the electric current flows along with the structures with low resistance (e.g., muscle, nerve and blood vessels) and eventually cause severe head injury in those with high resistance (e.g., skin, ligament, and bony tissue). In this situation, muscle, skin, tendon, fat, and bone are susceptible to an irreversible injury, both at the entry and exit sites tend to produce more extensive tissue damage [5]. Therefore, the severity of the injury is not reflected in the appearance of the external lesion. HVEB are devastating injuries associated with a vast array of serious and inevitable complications. The prognosis for these patients depends on the degree of the initial insult as well as the severity of any subsequent complications [6]. Accordingly, the delayed thrombosis of the major vessels of upper extremities was found to be more frequently injured than lower extremities [7]. Clinical presentations are variability and leading to non-viable extremity amputation and intractable complex defect with sepsis and increased mortality, that a prolonged serial of debridements should be revised until the entire wound acquires a bed of fresh granulation tissue for the flaps or skin grafts. Early intervention is the goal of resuscitation and surgery being the mainstay of management.

NPWT for wound healing

NPWT is a non-invasive treatment that uses a vacuum to increase blood supply to the wound, stimulating angiogenesis and formation of granulation tissue, the proliferation of fibroblasts and endothelial cells [8], also decrease the bacterial load, reduce swelling and decrease exudate while maintaining a moist environment that facilitates wound healing [9].

The systemic mobilization of various cells during NPWT may be a mechanism for healing intractable wounds with infections or skin defects *via* the formation of increased granulation tissue with numerous small blood vessels [10]. Oxygen partial pressure of wound surface could be reduced significantly by NPWT, which better for vascularization by enhancement of HIF-1α and Vascular Endothelial Growth Factor (VEGF) [11]. NPWT also promotes the expression of VEGFR2 and VEGFR3, which increases VEGF receptor combination to accelerate wound healing [12]. NPWT reduction of bacterial burden in wound with moderate or high levels of colonization. The authors' findings suggest BFBM dressings may be a WCL of choice during the treatment of chronic wounds with [13]. NPWT may increase the cellular antioxidative stress reaction and inhibit the reactive oxygen species as well as the inflammatory mediators to degrade the inflammatory response [14].

Bone marrow and bone marrow aspirate

Various adult organs and tissues harbor stem and progenitor cells that could potentially be used to repair, regenerate, and restore a variety of different tissues following acute injury or tissue destructive diseases, such as bone marrow and peripheral-blood are both regular transplantation source for stem cell therapy [15]. These cells not only participate in the regeneration process by differentiating into

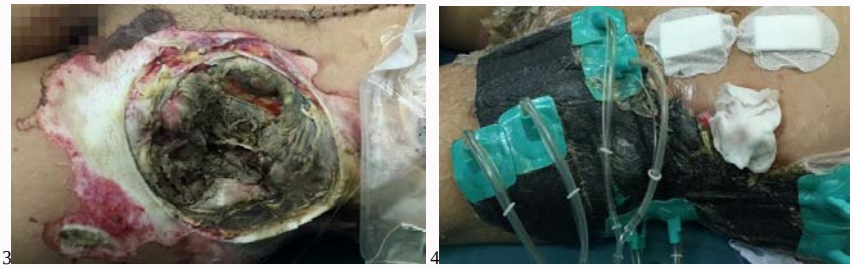
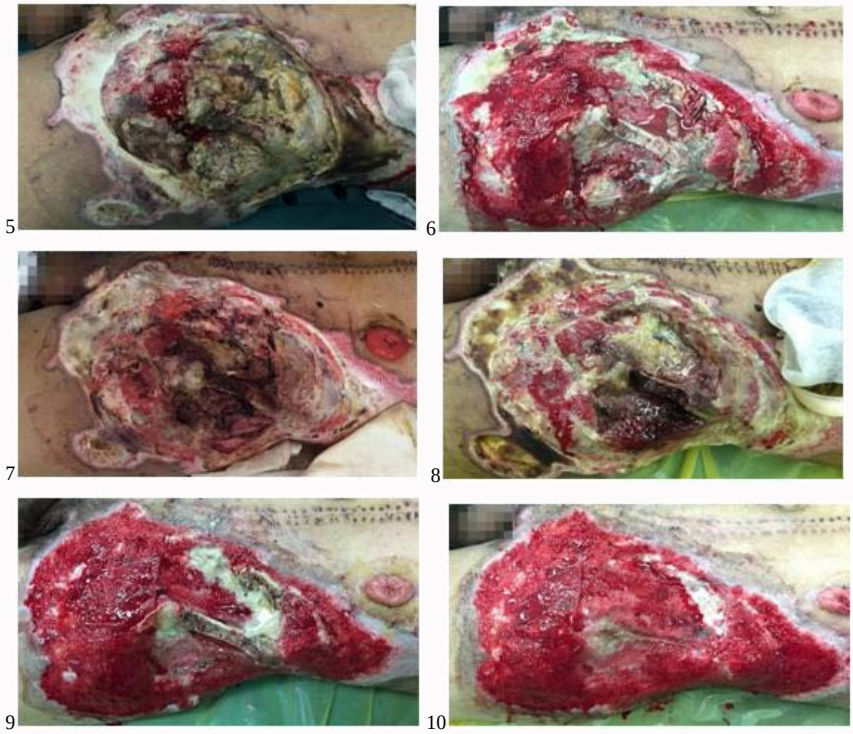


Figure 3 and 4: Progressive tissue necrosis of the hypogastric defect. After performing a consecutive wound observation and complete status assessment, axilla amputation and iliac osteotomy with NPWT had performed on 3rd DOA.



Figures 5-10: Potential stem cell therapy of autologous iliac bone marrow aspirate and injection at the poor granulation tissues had performed during the operations for 6 times, on 10th, 15th, 19th, 24th, 29th, 36th DOA individually, and complex defect wound was amazing healing stringendo without a flap coverage.

tissue-specific cell types but also promote endogenous tissue repair by secreting a multitude of trophic factors [16].

The bone marrow is an important source of hematopoietic stem cells that regularly regenerate components of the blood, and non-hematopoietic stem cells, including Mesenchymal Stem Cells (MSCs). There have been reports proving the plasticity of the stem cells harvested from the bone marrow and its ability to convert into many cell lines. There were no statistically significant differences in cell characteristics between MSCs cultured from the sternum and the ilium under any circumstances [17]. Currently there are many evaluations and clinical applications on bone marrow aspirate have emerged, that application of autologous bone marrow aspirate and cultured bone marrow cells had significantly higher percentage reduction of wound size compared to freshly applied bone marrow aspirate [18]. The ilium is the preferred donor site for obtaining autologous stem cells at the point of care. The tibial plateau yielded only half as much bone marrow multipotent or progenitor stem cells as did the anterior and posterior ilium [19], and the yield of colony-founding connective-tissue progenitors was 1.6 times greater in the posterior compared with the anterior iliac crest [20], but only 5 ml to 10 ml aspirates is enough for adequate numbers of MSCs [21,22]. There will be an easier and safer way for the clinical application of fresh iliac autologous bone marrow aspirate and injection than those cells from peripheral-blood, sternal and cultured under the protocol [23,24]. By using this similar technique, adult stem cells will be easily harvested through fairly non-invasive procedures, not just musculoskeletal tissues [25].

Stem cells therapy for wound healing

Adult stem cells have long been discussed in regards to their application in regenerative medicine. Adult stem cells have generated a great deal of excitement for treating injured and diseased tissues due to their impressive capabilities to undergo multi-lineage cell differentiation and their self-renewal ability. Most importantly, these qualities have made them advantageous for use in autologous cell transplantation therapies. Tissue engineering and cell therapy approach aims to take advantage of the repopulating ability and plasticity of multipotent stem cells to regenerate lost or diseased tissue. Researchers continue to investigate stem cells in mature

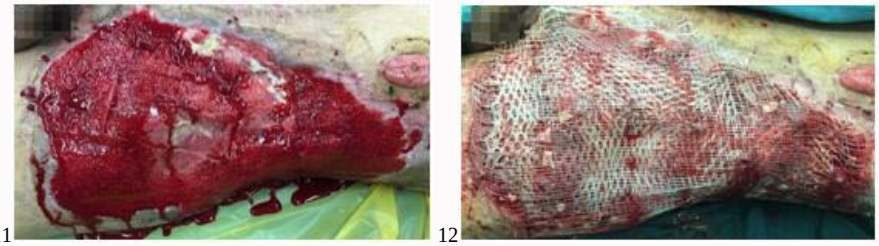


Figure 11 and 12: Granulation tissues were fresh and achieve the condition for mesh skin autografts on 42th DOA.

tissues and demonstrate the potential ability of organ-specific cells to differentiate into multiple lineages [26].

With the increasing evidence to prove the usefulness of stem cell therapy in wound healing, the focus of research is shifting toward modalities to optimize cell delivery that can promote the wound repair process through differentiation and release of proangiogenic factors. It is speculated that MSCs mobilize from the bone marrow niche and migrate to hypoxia and ischemic tissue through the peripheral circulation in response to cytokine signaling by injury and release factors that modulate repair indirectly by mobilizing the host cells and attracting them to the injury site in a paracrine manner. After reaching the site of injury, they differentiate into various cells for advance proliferation, angiogenesis and remodeling. Transplanted stem or progenitor cells improve tissue healing and regeneration anatomically and functionally, mostly due to their secreted trophic factors, such as VEGF stimulated human umbilical vein endothelial cell proliferation, monocyte chemoattractant protein-1 (MCP-1) elevated macrophage migration and interleukin-6 (IL-6) increased IgM production [27]. In addition to direct cell replacement using stem cells, the stem cell extractive has improving the effect of wound healing with intercellular molecule exchange by stem cell secretory factors to reducing tissue damage and augmentation of endogenous repair [28,29]. This process is loosely called a 'paracrine mechanism', but its effects are not necessarily restricted to the injury site [30]. And study provides direct unprecedented evidence for a paracrine lymphangiogenic action of BM-MSC *via* the production of VEGF-A which acts on LEC VEGFR-2 [31]. Meanwhile, both *in vivo* and *in vitro* findings demonstrate that the α6 integrin subunit in BMSCs is important for their ability to stimulate vessel morphogenesis to promote angiogenesis [32]. Not only have stem cells been shown to promote better and faster healing by paracrine, but also they have the ability to decrease the inflammation levels with less scar progression and fibrosis [33].

Potential mechanism of NPWT and stem cell combinatorial therapy

Wound healing is a complex process which depends on the presence of various types of cells, growth factors, cytokines and the elements of the extracellular matrix. Most of the cells that contribute to the repair process are indeed chemo-attracted to the injury site, potentially through host neo-angiogenesis. Angiogenesis or neovascularization is a critical component of wound healing as it is necessary to supply oxygen and nutrients to and carry waste away from the damaged tissue [34]. Therefore, stem cells, which give rise to their early descendants' progenitor cells and subsequently differentiated cells, play a specific role in the process of wound healing. The activity of these cells is strictly regulated by various growth factors, especially VEGF, which was verified that the transplantation

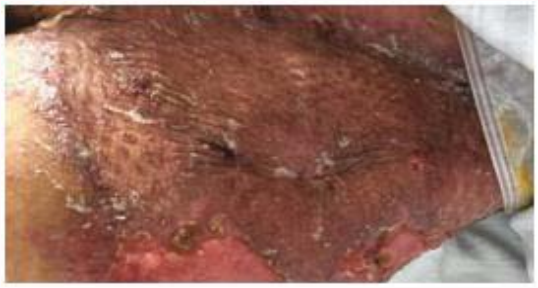


Figure 13: Wound healing satisfactorily on 70th DOA.

of VEGF-expressing stem cells improved repair through modulation of angiogenesis, regeneration, and fibrosis, too [35]. Some preclinical results indicate that a short time treatment with NPWT, can enhance cellular proliferation of stem cells and induce the differentiation [36], and may act as an inductive role to enhance angiogenic capacity when stem cells were injected may serve as a simple and efficient clinical solution for complex defects [37].

Microenvironment: The existence of a stem cell niche as a spatially confined regulatory entity relies on the notion that stem cells and progenitor cells are strategically positioned in unique bone marrow microenvironments with defined anatomical and functional features. The capability to engineer microenvironmental cues to direct a stem cell population toward multiple fates or behaviors' change; However, harsh conditions at the site of the wound, including hypoxia, ischemia, oxidative and inflammatory stress, increased fibrosis and insufficient angiogenesis, and in some cases immunological response incompatibility, are detrimental to stem cell survival [38]. And most stem cells are in a partially reprogrammed state of pluripotency, which is generated by the injured microenvironment modification [39].

Stimulation: *In vitro* study findings highlight an important role for cyclic mechanical loading preconditioning of donor stem cells in optimizing transplantation, that mechanically stimulated stem cells displayed higher VEGF expression than non-stimulated cells [40]. And, the beneficial effects of mechanical stimulation on stem cells mediated repair are lost by inhibiting VEGF [41].

HIF-1α pathway: Hypoxia also modulates the expression of soluble mediators and cytokines, as well as that of their receptors. Hypoxia-inducible factor 1α (HIF-1α) is known to regulate the expression levels of key metabolic enzymes that favour lactic acid fermentation over mitochondrial respiration. HIF1α activity leads to the secretion of VEGF, a regulator of stem cell function. *In vitro*, stem cells are better maintained in hypoxic culture conditions, possibly owing to lower cycling rates. *In vivo*, inducible deletion of HIF1α in

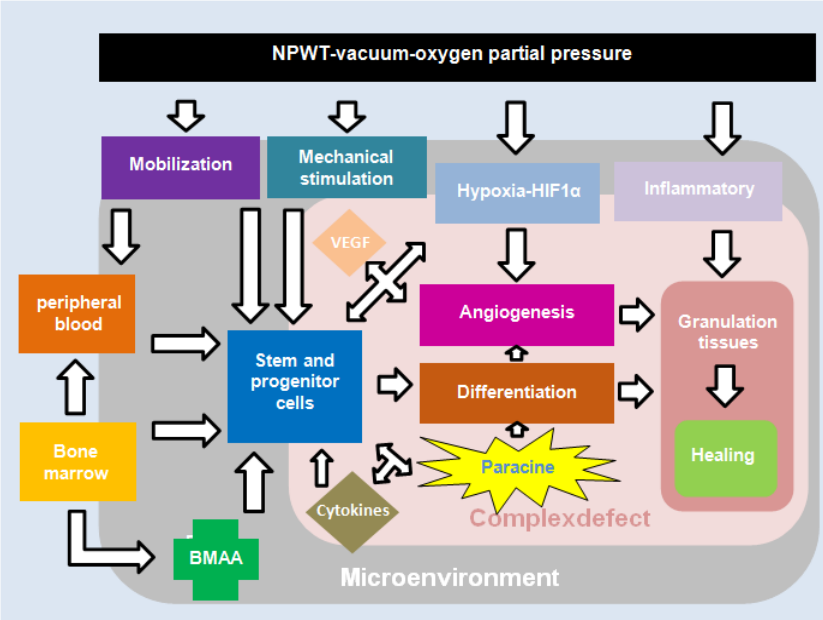


Figure 14: Potential mechanism of combinatorial therapy.

stem cells leads to decreased quiescence and a better reconstitution ability. Thus, hypoxia might be an important step in the ontogeny of cellular niches within the bone marrow [42]. But the characteristic hypoxic state of stem cells is not solely [43].

Conclusion

In which complex defect won't be achieved successfully, attempts are made to convert the wound bed into the environment where maximum wound healing can be achieved [44]. As autologous bone marrow aspirate therapy in wound healing helps in wound bed preparation to allow the wound to heal completely or cover by a skin graft or flap [45]. Compared with those conventional methods, the combination of NPWT and potential stem cell therapy appears to be a safer and more effective method for granulation tissue growth and reduces the surgical burden for complex defect patients. Additionally, this report describes the successful use of this method as a stand-alone treatment for both complex defect closures. We are tempting to hypothesize that the promotion of tissue repairs mainly *via* neo-angiogenesis by iliac bone marrow-derived stem cells (Figure 14). For non-vascularized tissues, such as articular cartilage, the regenerative property of the injected stem cells still promotes a paracrine, or bystander, effect, which involves the resident cells found within the injured microenvironment, which is very important for stem cells survival and pluripotency.

Successful cell transplantation will require optimizing the best cell type and site for engraftment, overcoming limitations to cell migration and tissue integration, and occasionally needing to control immunologic reactivity, as well as a number of other challenges. Collaboration among scientists, clinicians, and the industry is critical for generating new stem cell-based therapies [46]. However, the biological mechanisms behind the beneficial effect of the combination are still unclear and require further investigation using animal models and potentially randomized, human clinical studies.

Future Direction Potential

We postulate on novel and future uses for NPWT, including application in targeted drug delivery, stem cell therapy, and the prospect of combination with filtration devices, adaptable smart dressings, and remote monitoring [47]. In stem cell therapy, the new source of induced Pluripotent Stem Cells (iPSCs) have practically unlimited proliferation potential and a capability to differentiate into any cell type in the human body they are an attractive source of cells for regenerative medicine [48]. But numerous ethical, technological, and regulatory complications have been hampering PSC use in clinical applications. We need to reduce the risks associated with them and find possible solutions for successful use in the clinic [49].

Most of the wound healing process in mammalian adults leads to a compromise in the quality of healing ultimately and always result in scar formation [50]. It can cause pain and loss of function in the afflicted tissues [51]. There are also psychosocial ramifications associated with a scar formation on exposure skins, as even small changes in scar appearance can significantly impact patient quality of life [52]. Scarring results from injuries and disease. How to archive scarless healing will be a hot topic in the future.

Although we recognize the many advantages of improved musculoskeletal health, we also note that our ability to sustain this health and to maintain the quality of life in an aging population is currently deficient. However, global efforts have produced numerous advances in tissue engineering and regenerative medicine that will collectively serve to fill this deficiency in the near future [53].

Stem cells (either embryonic or induced) sometimes develop mutations in tumor-suppressor genes *in vitro* [54]. To ensure that the emerging field of stem-cell therapy fulfills its promise to patients, we must first understand its risks and benefits and develop therapeutic approaches based on sound science, which requires a commitment to the principles of evidence generation [55]. Researchers will have to pay close attention to evaluate which cell selection works best for a given disease. In addition, once a stem cell type has been selected for a therapeutic treatment, researchers must work to overcome any relevant obstacles, whether they are tumorigenicity, immune-rejection, or incomplete differentiation [56]. The U.S. biotechnology

and pharmaceutical industries arguably lead the world in innovation while operating under stringent regulations set by the Food and Drug Administration (FDA) [57,58].

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Authors' Contributions

Fan Yang makes substantial contributions to conception and design; participate in drafting manuscript and graphing.

Xiangjun Bai participates in drafting manuscript.

Xiaojing Dai participates in collect related reviews and classification.

Keith Kenter participates in revising it critically for important intellectual content.

Yong Li give final approval of the version to be submitted and any revised version.

Acknowledgment

The authors thank the Bai medical team for the effective teamwork. We also thank Dr. Li's Laboratory members for valuable discussions. We sincerely apologize for the inadvertent omission of any pertinent original references owing to space constraints.

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