How I treat refractory chronic graft-versus-host disease

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Tehran-Ismoh , 6 januray 2022

Introduction

- With > 30 000 allogeneic transplantations performed worldwide each year and 35% to 50% of recipients developing cGVHD, this complication remains a frequent and formidable foe.
- > 20% of patients with cGVHD achieve a durable partial (PR) or complete response (CR) and survive 1 year after initial therapy without additional systemic therapy, indicating that treatment refractory cGVHD is relatively common and patients likely will require ongoing therapy.

Clinical manifestations of chronic GVHD

Organ or site	Diagnostic (sufficient for diagnosis)	Distinctive (insufficient alone for diagnosis)	Other	Features seen in both acute and chronic GVHD
Skin	Poikiloderma Lichen planus-like Sclerosis Morphea-like Lichen sclerosis-like	Depigmentation Papulosquamous		Erythema Maculopapular Pruritus
Nails		Dystrophy Onycholysis Nail loss Pterygium unguis		
Scalp and body hair		Alopecia (scarring or nonscarring) Scaling		
Mouth	Lichen planus-like	Xerostomia Mucoceles Mucosal atrophy Pseudomembranes or ulcers*		Gingivitis Mucositis Erythema Pain
Eyes		New dry, gritty, or painful eyes (sicca) Keratoconjunctivitis sicca Punctate keratopathy		
Genitalia	Lichen planus-like Lichen sclerosis-like Female: Vagina scarring or stenosis	Erosions* Fissures* Ulcers*		

Clinical manifestations of chronic GVHD

	Vagina scarring or stenosis Clitoral or labial agglutination Male: Phimosis Urethral scarring or stenosis			
GI tract	Esophageal web Esophageal stricture			Diarrhea Anorexia Nausea or emesis Failure to thrive Weight loss
Liver				Total bilirubin, alkaline phosphatase or ALT >2× ULN
Lung	Bronchiolitis obliterans diagnosed by biopsy BOS§		Cryptogenic organizing pneumonia† Restrictive lung disease†	
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures due to sclerosis	Myositis Polymyositis		
Hematopoietic and Immune			Thrombocytopenia Eosinophilia Hypo- or hypergammaglobulinemia Autoantibodies Raynaud phenomenon	
Others			Effusions‡ Nephrotic syndrome Myasthenia gravis Peripheral neuropathy	

The frequency of organ involvement

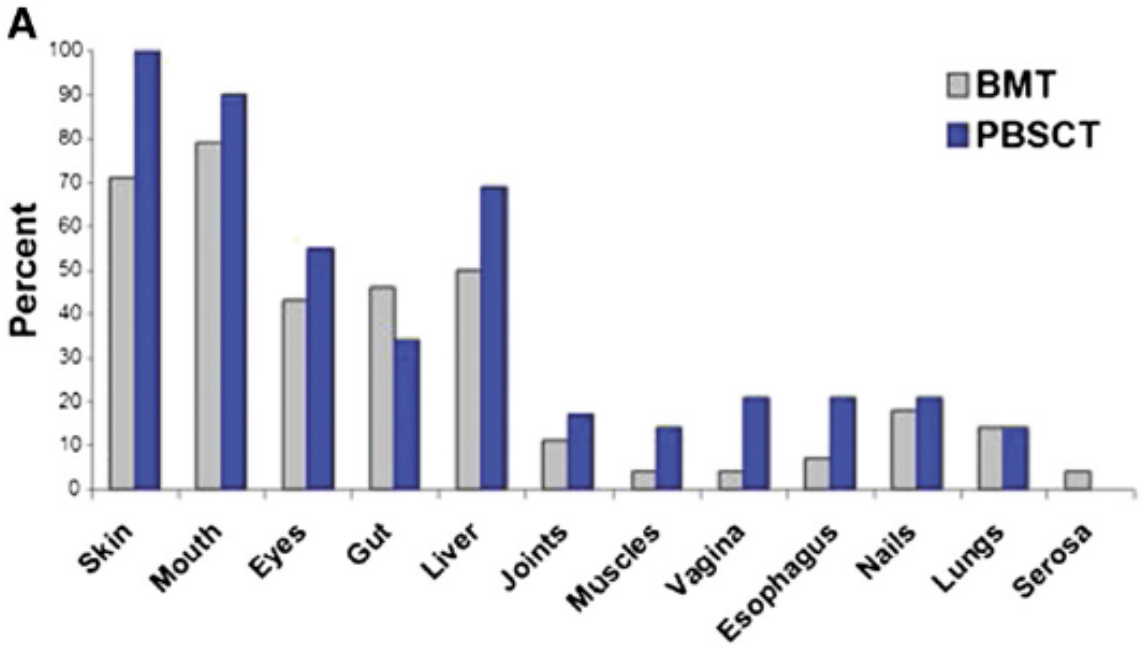
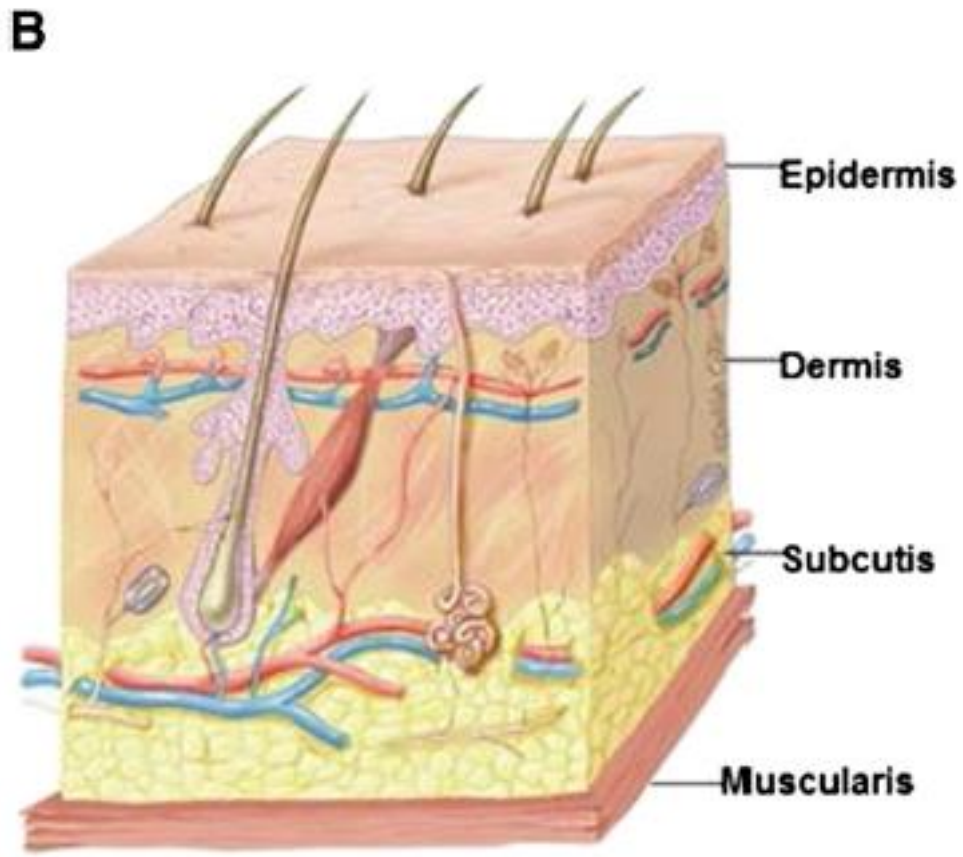


Figure 1. The frequency of involvement by chronic GVHD varies across organs and sites and is higher after HCT with mobilized blood cells as compared with marrow. (A) The most frequently involved organs and sites are the skin, mouth, eyes, gastrointestinal tract, and liver.[3] (B) Chronic GVHD can affect all layers of the skin. Photographs of each manifestation in italic may be found in the supplemental Data, available on the *Blood* Web site. Artwork by Delilah Cohn, MFA, CMI, used with permission.

Chronic GVHD can affect all layers of skin



Manifestations

- *Lichen planus-like feature*
- *Lichen sclerosus-like*
- *Poikiloderma*
- *Keratosis pilaris*
- Depigmentation
- Alopecia

- Dermal sclerosis
- Edema (early fasciitis / early sclerosis)
- *Deep Sclerosis*
- Fasciitis
- Myositis

Evaluation and frequency of monitoring according symptoms or affected organs

Review of systems (see Table 3 for chronic GVHD-specific questions)	Every clinic visit	Every clinic visit
Physical examination		
Complete skin examination (look, touch, pinch)	Every clinic visit	Every clinic visit
Oral examination	Every clinic visit	Every clinic visit
Range of motion assessment	Every clinic visit	Every clinic visit
Performance score	Every clinic visit	Every clinic visit
Nurse assessment		
Weight	Every clinic visit	Every clinic visit
Height/adults	Yearly	Yearly
Height/children	Every 3-12 mo	Every 3-12 mo
Medical photographs	~100 d after HCT (baseline), at initial diagnosis of chronic GVHD, every 6 mo if skin or joints are involved and during treatment until at least 1 y after discontinuation of treatment	~100 d after HCT (baseline)
Other evaluations		
PFTs	~100 d after HCT (baseline); see also Table 4	~100 d after HCT and every 3 mo for the first year, then yearly if previous PFTs were abnormal or if continuing systemic treatment; reassess at onset of new symptoms
Nutritional assessment	As clinically indicated and yearly if receiving corticosteroids	As clinically indicated
Physiotherapy with assessment of range of motion	Every 3 mo if sclerotic features affecting range of motion until resolution	As clinically indicated
Dental or oral medicine consultation with comprehensive soft and hard tissue examination, culture, biopsy, or photographs of lesions, as clinically indicated	Every 3-6 mo or more often as indicated	Yearly
Ophthalmology consultation with Schirmer test, slit-lamp examination, and intraocular pressure	At initial diagnosis and every 3-6 mo or more often as indicated	~100 d after HCT (baseline) and yearly
Gynecology examination for vulvar or vaginal involvement	Every 6 mo or more often as indicated	Yearly
Dermatology consultation with assessment of extent and type of skin involvement, biopsy, or photographs	As clinically indicated	
Neuropsychological testing	As clinically indicated	
Bone mineral assessment (DEXA) scan	Yearly during corticosteroid treatment or if prior test was abnormal	~100 d after HCT if continuing corticosteroid treatment (baseline)

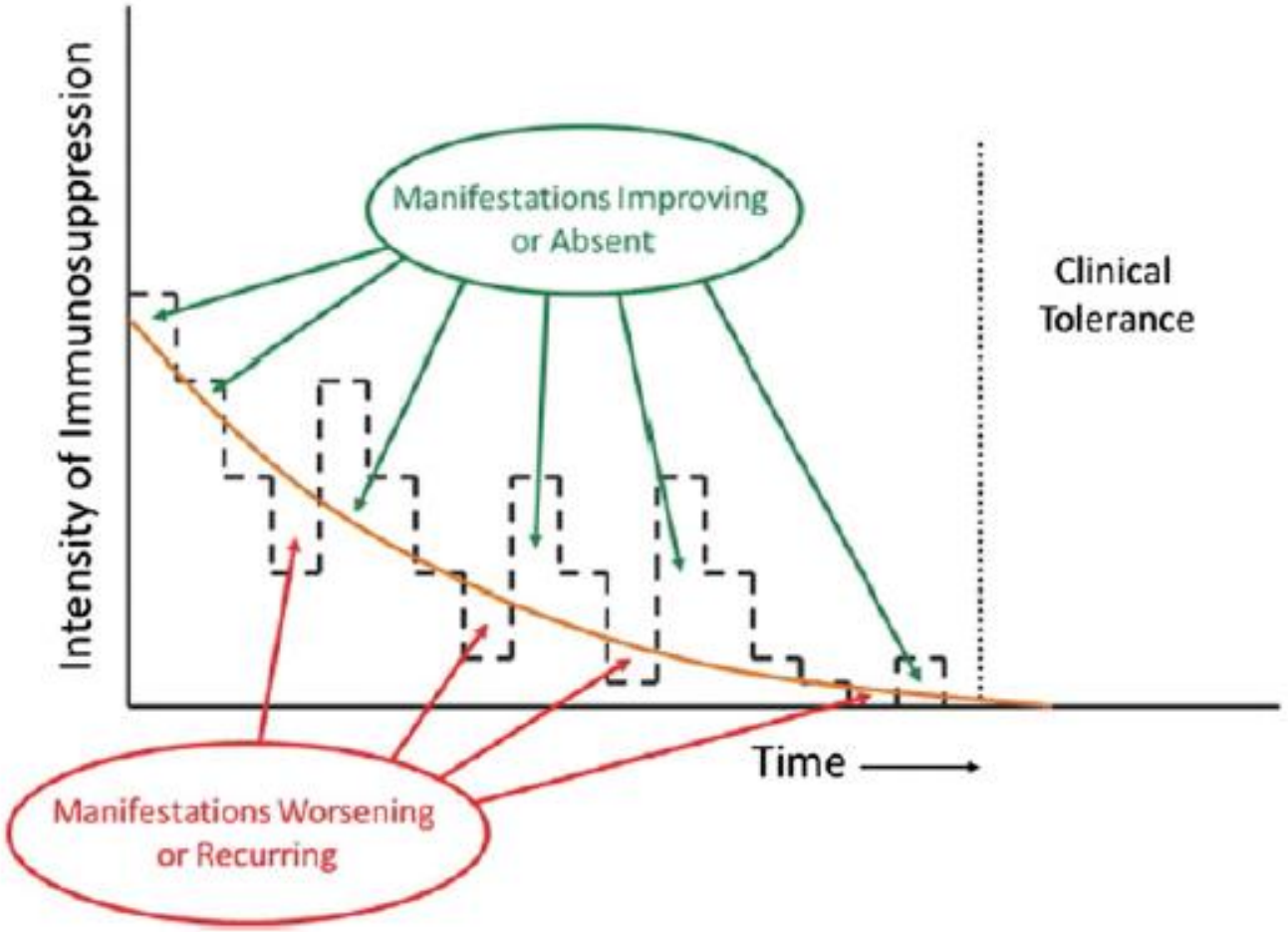
Chronic GVHD review of systems

No.	System/others	Inquire/description
1	Skin	Skin feels tight or hard, increased dryness, pruritus, or looks different (ie, new rash, papules, discoloration, shining scar-like, scaly)?
2	Sweat glands	Inability to sweat or to keep body warm?
3	Skin appendages	Loss of hair (scalp or body including bows or lashes), or nail changes (ridges or brittle, loss)?
4	Fasciae/joints	Stiffness or pain in the wrists, fingers, or other joints?
5	Eyes	Eye dryness, sensitivity to wind or dry environments (air conditioning), pain?
6	Mouth	Oral dryness, taste alterations, sensitivities (spicy/carbonate drinks, toothpaste), ulcers/sores, pain?
7	Esophagus	Foods or pills gets stuck upon swallowing?
8	Lungs	Cough, dyspnea (on exertion or rest) or wheezes?
9	Genital tract	Vaginal dryness, pain, dyspareunia (female); pain or dysuria due to stenosis of urethra (male)?
10	Weight loss	Unexplained weight loss or inability to gain weight (pancreatic insufficiency or hypercatabolism)?

Goal of GVHD treatment

- long-term goal of GVHD treatment is the development of immunologic tolerance, indicated by successful withdrawal of all immunosuppressive treatment without recurrence or clinically significant exacerbation of disease manifestations.
- The current therapeutic approach functions primarily to prevent immunemediated damage, while awaiting the development of tolerance.

Continuous recalibration of immunosuppressive treatment in order to avoid overtreatment or undertreatment.



Agents used for secondary treatment of chronic GVHD

Table 6. Agents used for secondary treatment of chronic GVHD*

Treatment	% Overall response*	Survival
ECP	65-70	70%-78% at 1 y
Rituximab	66-86	72% at 1 y
Imatinib	22-79	75%-84% at 1.5 y
Pentostatin	53-56	34%-60% at 1-3 y
Mesenchymal stem cells	50-74	78% at 2 y
Mycophenolate mofetil	26-64	67%-96% at 1 y
mTOR inhibitor	76	72% at 3 y
Interleukin-2	52	Not reported
Other therapies summarized in other reviews**		
Calcineurin inhibitor		
High-dose methylprednisolone		
Methotrexate		
Thalidomide		
Hydroxychloroquine		
Clofazimine		
Thoracoabdominal irradiation		
Alefacept		
Infliximab		
Etanercept[70]		

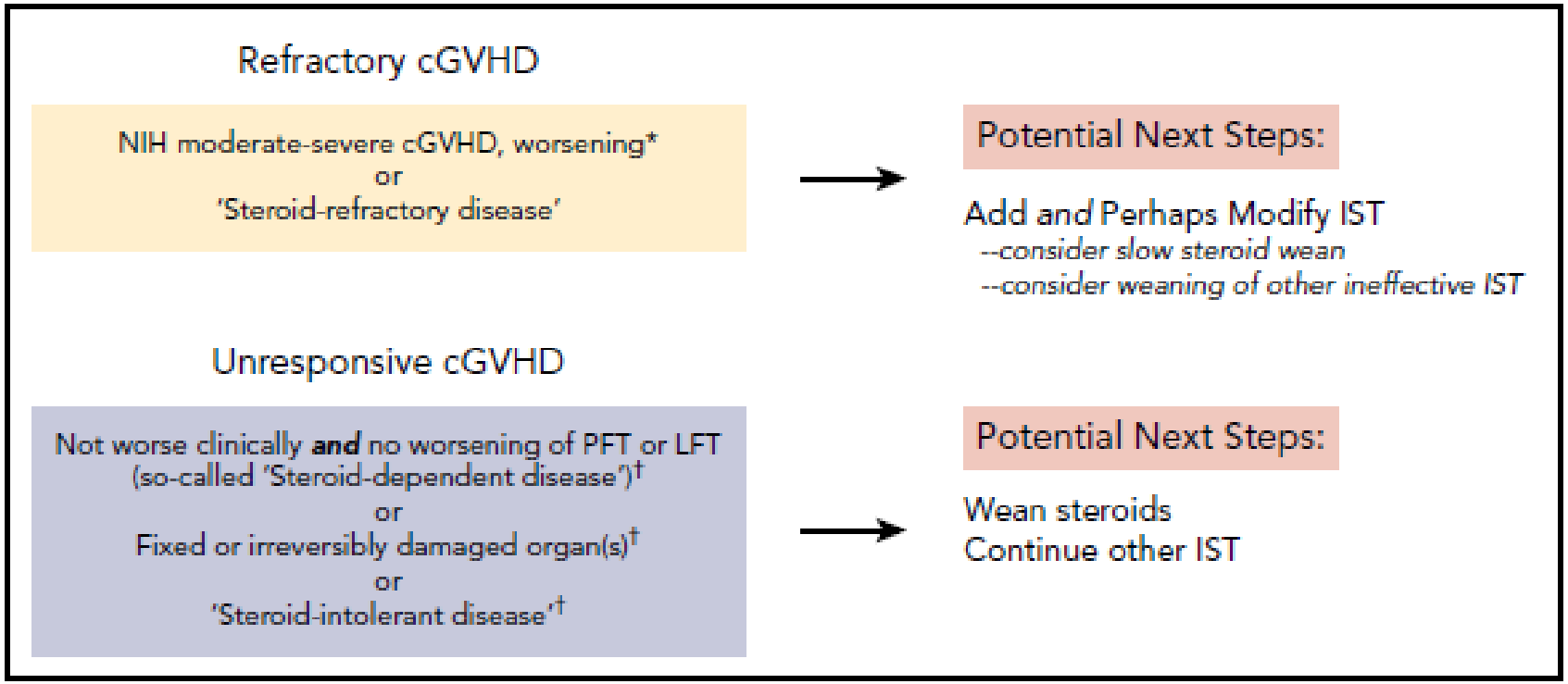


Figure 1. NIH global severity assessments to determine need for intervention in patients with ongoing cGVHD.[24,25] Our approach to patients seen in our multidisciplinary

Table 1. Adverse reactions of commonly used therapies in refractory chronic GVHD[14]

Agent	Potential major adverse effects (with major study citations)	Common (>10%) generally less severe adverse effects
Bortezomib	Peripheral neuropathy, thrombocytopenia, malignancy relapse[106]	Herpes virus reactivation
ECP	Vascular access complications[107]	Thrombocytopenia
FAM	New FDA MedWatch warning; warning only applies to azithromycin use in prophylactic (not treatment) setting[108,109]	
Ibrutinib (Imbruvica R)	Pneumonia,[29] impaired platelet function	Fatigue, muscle pain, peripheral edema
Imatinib		Peripheral edema
Interleukin-2	Injection site induration, infections[36]	Constitutional flu-like symptoms
MMF (Cellcept)	Viral reactivation, hypertension, pneumonia, posttransplantation lymphoproliferative disease[110]	GI toxicity, neutropenia, leukopenia
Pamolidomide	Tremor, muscle cramps, peripheral neuropathy[111]	Skin rash
Rituximab (Rituxan R)	Infection, late neutropenia[38,39,112]	B lymphopenia
Ruxolitinib (Jakafi R)	Viral reactivation/infection, bacterial infections[35]	Cytopenias
Sirolimus (Rapamune)	TAM when used in combination with calcineurin inhibitors, renal insufficiency,[113] proteinuria	Peripheral edema, hyperlipidemia, cytopenias

This list of agents represents a fraction of agents being actively evaluated. Preferred use of any agent still requires validation via larger clinical trials.

ECP, extracorporeal photopheresis; FAM, fluticasone, azithromycin, and montelukast; FDA, US Food and Drug Administration; GI, gastrointestinal; MMF, mycophenolate mofetil; TAM, transplantation-associated microangiopathy.

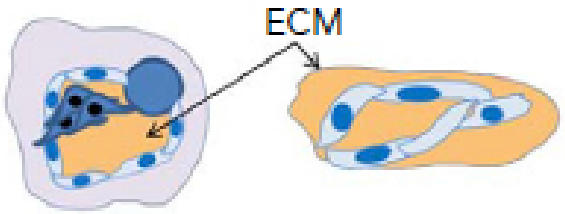
'Red Flag' Poor Prognostic Marker	Ongoing cGVHD Pathophysiology (histochemical patient/basic science data)	Additional Urgent Work-up
A *↓ Forced expiratory volume (FEV1) if FEV1/FVC <0.7 Hypoxia after 2 min. ambulation Dry cough, abnormal lung exam	Airway blockage and/or constriction  	High resolution expiratory chest CT Scan Diagnostic Bronchoscopy (rule out infection)
B *↑3x normal Total Bilirubin (T. bili) *↑3x normal Alkaline phosphatase (Alk Phos, AP)	Biliary Duct 'withering and drop-out' 	Serum PCR tests for viruses (CMV, HSV, adeno, EBV, Hepatitis virus if indicated) Consider liver biopsy to rule out drug toxicity or infection
C * >10% weight loss Acute diarrhea	Mouth ulcerations → precludes eating Esophageal strictures Lower gut GVHD	PCR of feces for enteroviruses Endoscopy
D ↓Platelets	Immune attack → Bone marrow, Thymus, Secondary lymph organs 	Plasma virus Blood culture Bone marrow biopsy

Figure 2. Assessment of worsening cGVHD reflective of cGVHD pathophysiology that requires urgent attention. (A) Decrease in FEV1 may reflect pathology of

- Ibrutinib demonstrated clinical improvement in> 65% of patients when administered in the landmark trial to patients with steroid-refractory GVHD with oral or skin disease.
- Although evidence is lacking, use of rapamycin for joint involvement, tacrolimus for myositis, and ruxolitinib for scleroderma can be effective.
- ECP for steroid-refractory skin disease, especially sclerodermatous cGVHD.

- The median duration of systemic treatment of chronicGVHDis;2 years in patients who had HCT with marrow cells and ;3.5 years in those who had HCT with mobilized blood cells.

- Currently, the choice of therapy after failure to achieve PR or CR with initial treatment remains patient specific, with comorbidities and history of infectious complications heavily influencing agent choice.
- These factors, coupled with organ function, toxicities of agents , patient preferences, and provider experience, collectively determine the preferred next agent.

Future perspectives

- Participation in a clinical trial represents the first option to consider for eligible patients with chronic GVHD.
- Novel strategies directed toward depleting or modulating B cells, expanding T or B regulatory cells, and targeting the processes implicated in fibrosis are under active investigation and could lead to future advances in treatment of chronic GVHD.

Human placental mesenchymal stromal cell-derived exosome-enriched extracellular vesicles for chronic cutaneous graft-versus-host disease

A case report

BACKGROUND

- Human mesenchymal stromal cells (hMSC) have been used to treat many inflammatory diseases/disorders in the clinic.
- A recent systematic review and meta-analysis showed that treatment wit these cells is not associated with any severe or notable side effects.
- Furthermore, placenta cells lack MCH class II antigens, which are responsible for allograft rejection.

BACKGROUND

- Exosomes are natural extracellular vesicles released by different cell types and contain proteins, lipids and RNA.
- These vesicles have been known to participate in intercellular interactions and communications.
- Depending on the origin and microenvironment of exosomes, they could play different roles, of which immune modulation is one of the most important ones.

METHODS AND PATIENT

2.1 | Cell isolation

hPMSCs derived from human placenta (single donor) tissue were isolated and identified by the method has been described by Pelekanos et al.[12] Also, the donor's blood sample was negative for viral infections including mycoplasma, cytomegalovirus (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) evaluated by polymerase chain reaction (PCR). The cells exhibited surface expression of mesenchymal markers (CD73, CD 105, CD90 and CD 44; Figure S1) and were negative for haematopoietic markers (CD45, CD 34 and HLA-DR) identified as hPMSCs. Also, the cells at passages 2–3 were assessed for osteogenic, adipogenic and chondrogenic differentiation potentials.

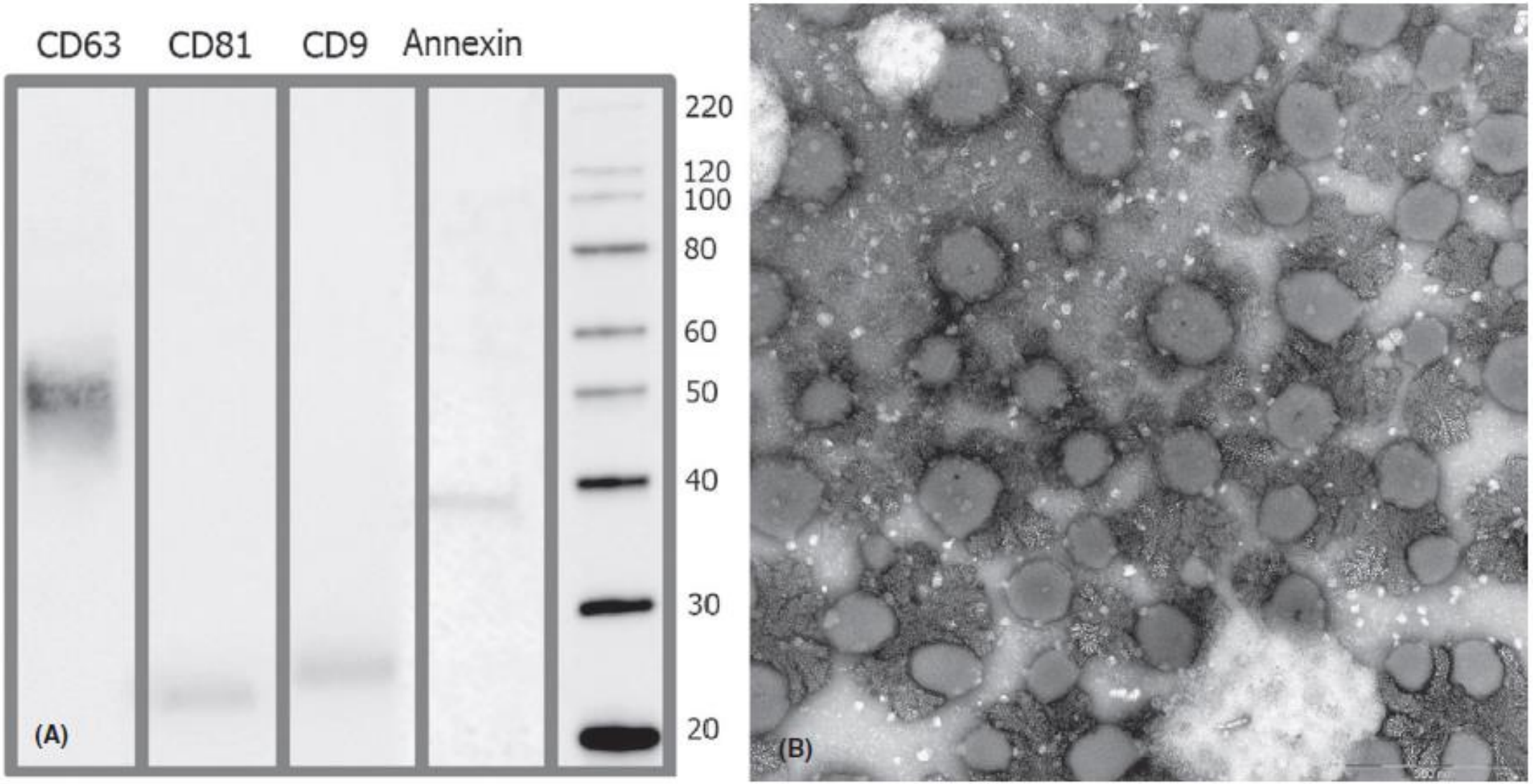


FIGURE 1 (A) Western blot analysis of purified extracellular vesicles. The lines are showing CD63, CD81, CD9 and annexin as markers for extracellular vesicles form the human placental mesenchymal stem cells. Numbers. (B) Transmission electron microscopy of purified exosomes-enriched extracellular vesicles

Received: 8 August 2021 | Revised: 7 November 2021 | Accepted: 19 November 2021

DOI: 10.1111/jcmm.17114

SHORT COMMUNICATION

WILEY

Human placental mesenchymal stromal cell-derived exosome-enriched extracellular vesicles for chronic cutaneous graft-versus-host disease: A case report

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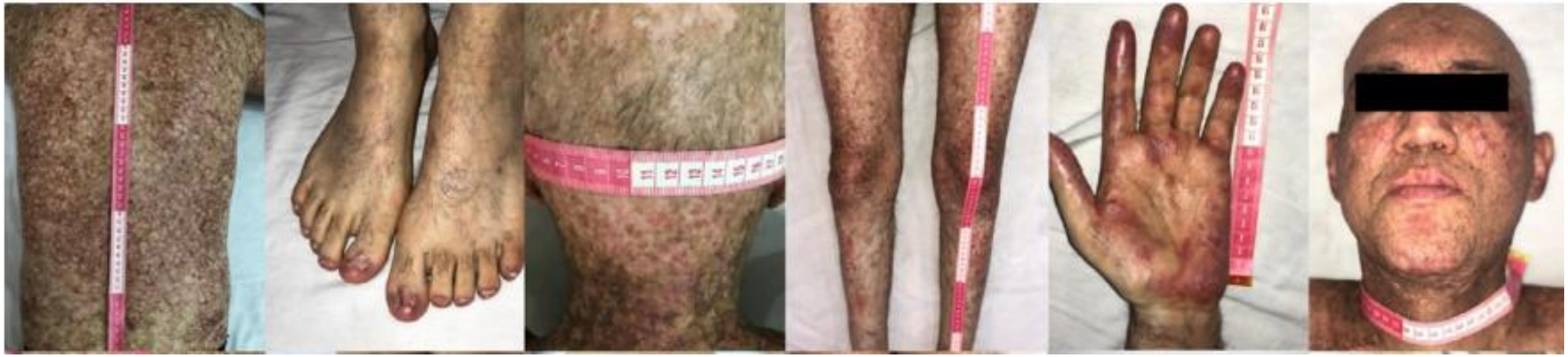
Keywords: cutaneous GVHD, exosome, graft-versus-host disease, human mesenchymal stromal cell

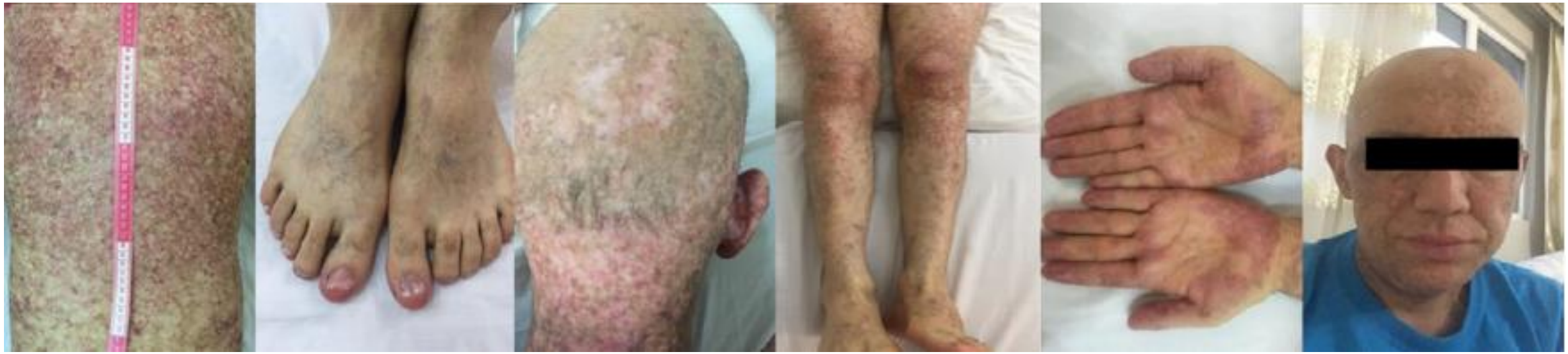
3 | CASE PRESENTATION

The patient was a 39-year-old Caucasian male diagnosed with AML type M4 5 years ago (April 2016). Following routine treatments and after reaching complete remission, he underwent PBSCT (one session) from an identical donor (brother). After the transplantation, he presented with acute gastrointestinal (GI) GVHD on a prophylaxis immune suppression regime, with his symptoms and signs brought under control through increasing corticosteroid and cyclosporin dosages. After a year, the cutaneous cGVHD started, which did not respond to extracorporeal photopheresis (12 sessions), tacrolimus, imatinib and high-dose corticosteroids. Also, during the last 18 months, the patient was receiving 5 mg per day of prednisolone and 50 mg and 25 mg per odds and even days (respectively) of cyclosporine for 18 months.

Cutaneous chronic graft-versus- host disease in the patient. pictures represent before the extracellular vesicles therapy



Cutaneous chronic graft-versus- host disease in the patient. pictures represent after 4 ,extracellular vesicles therapy



DISCUSSION

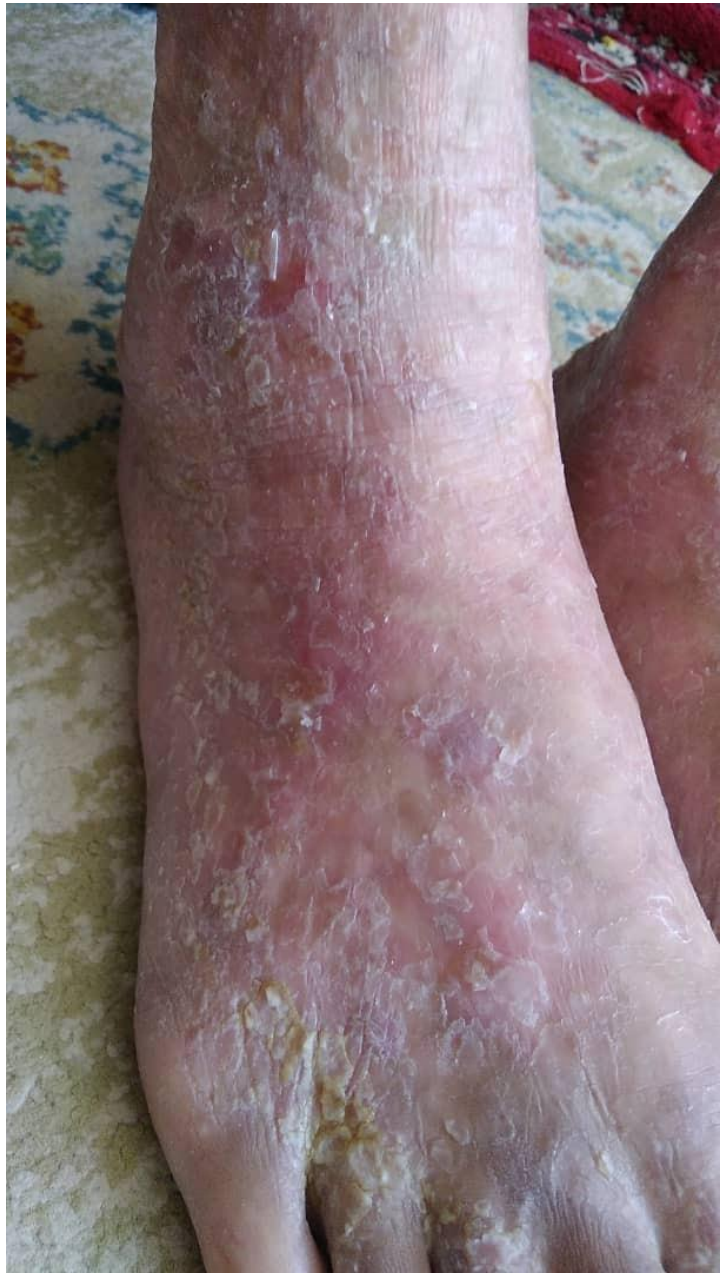
- It was shown that the mentioned treatment could decrease the signs and symptoms caused by cutaneous cGVHD, specifically hyperpigmentations and ulcers caused by skin dryness.
- Also, the cutaneous inflammation decreased significantly and was more evident than other manifestations due to the anti-inflammatory potential of the treatment.

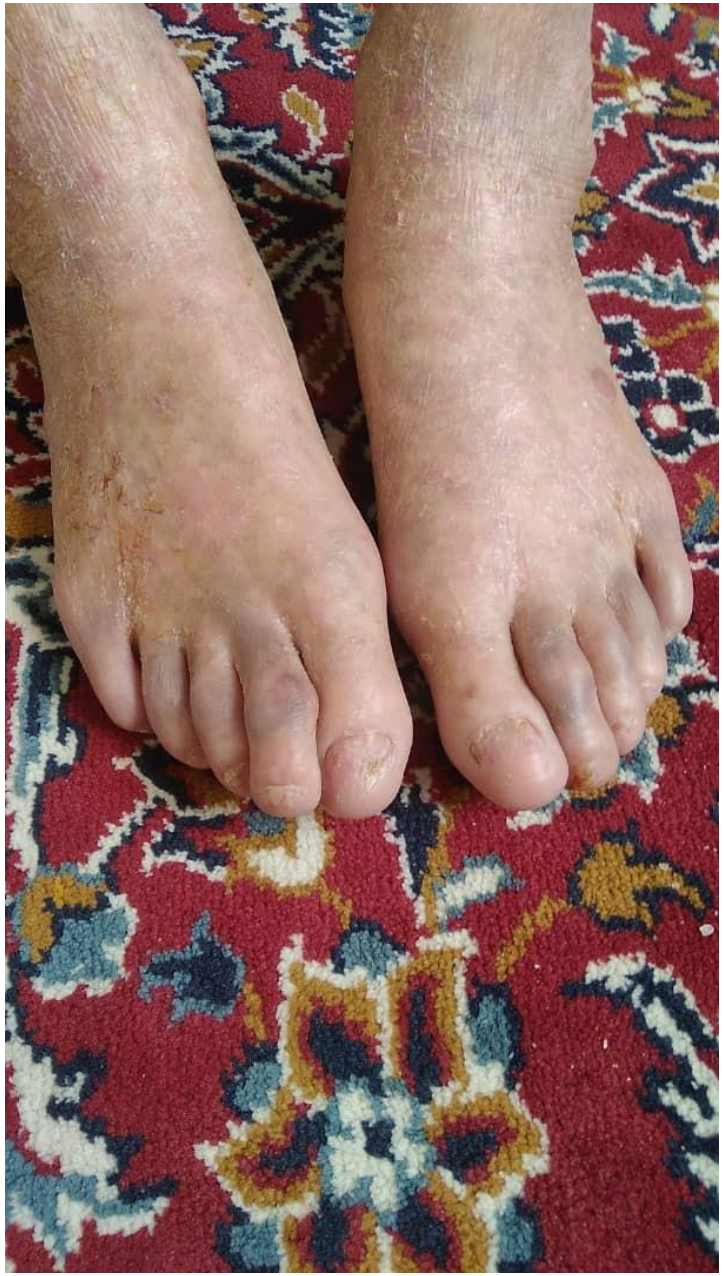
Laboratory variables before and 4 weeks after the last session of intervention

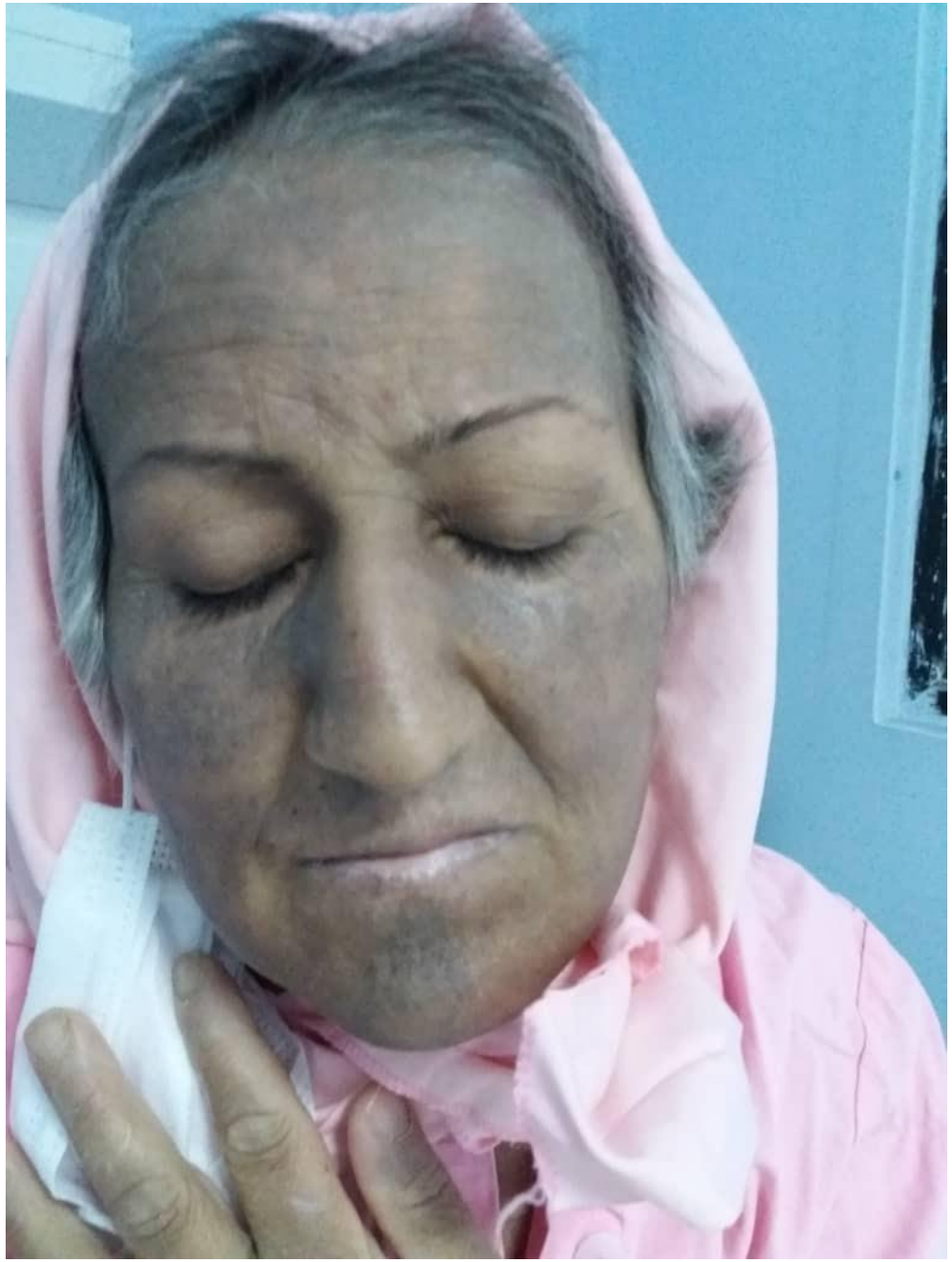
Variable	Before treatment	After the fourth intervention
White blood cells/mm^3	6830	7800
Neutrophils/mm^3	2049	3666
Lymphocytes/mm^3	3346	3588
Monocytes/mm^3	1229	390
Eosinophils/mm^3	204	2
Haemoglobin gr/dl	17.7	17.3
Haematocrit (%)	51.1	48.3
Platelet $\times 10^3/mm^3$	225	228
C-reactive protein	1+	Negative
Erythrocyte sedimentation rate (mm/h)	23	10
Creatinine mg/dl	0.8	0.9
Aspartate transaminase IU/L	59	57
Alkaline transaminase IU/L	50	59
Alkaline phosphatase U/L	333	365
Total bilirubin	0.8	0.8
Direct bilirubin	0.4	0.4
Lactate dehydrogenase U/ml	482	461

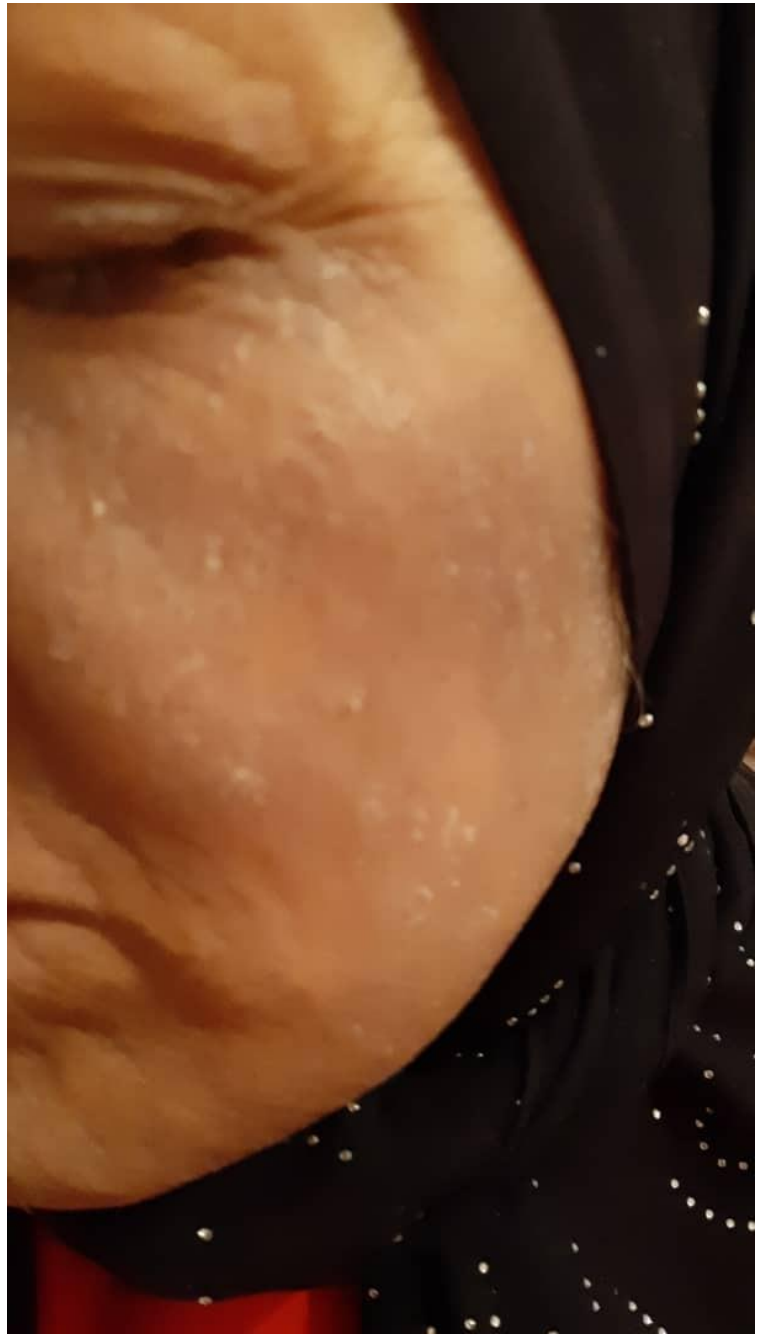
DISCUSSION

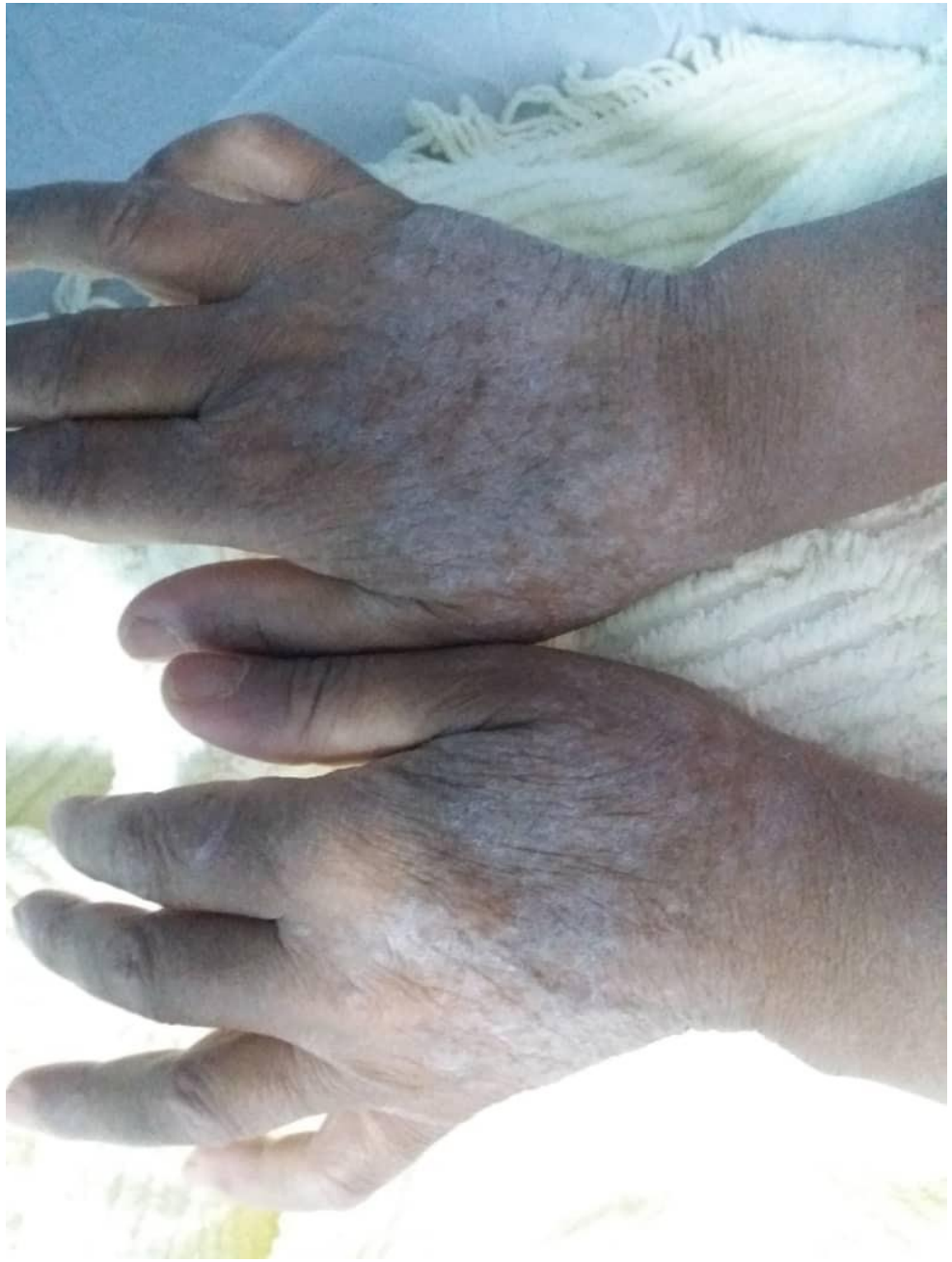
- As shown in Table , monocytes have been decreased from 18% to 5%, which is clinically significant.
- It has been shown that donor monocytes could be involved in the pathogenesis of GVHD.
- In patients diagnosed with GVHD, it has been shown that the intermediate CD14++ CD16+ monocytes could promote the induction of a subset of Th17 glucocorticoid resistance cells.
- Thus, it seems that our intervention was able to reduce this effect in our patient who did not respond to corticosteroid therapy.

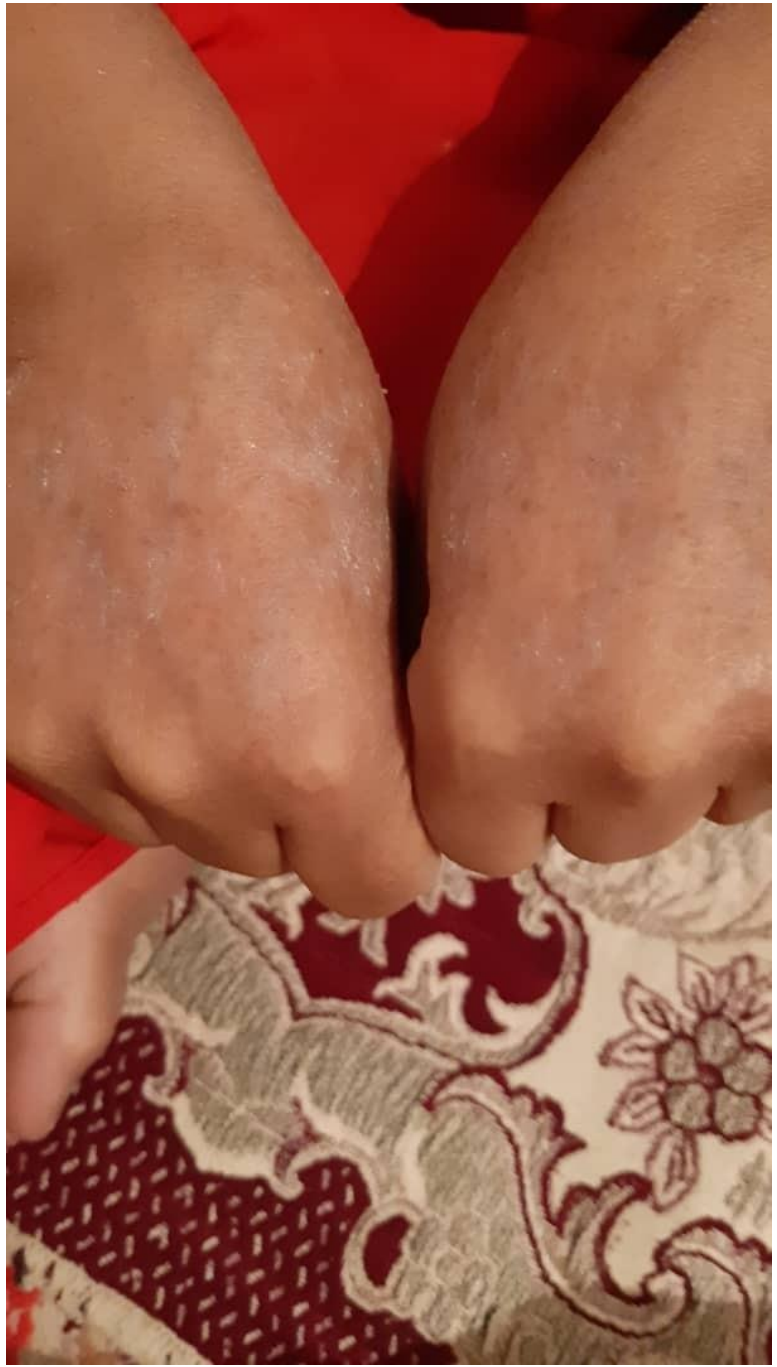












DISCUSSION

- To our knowledge, we are reporting the second case of exosome therapy for GVHD in a cutaneous cGVHD patient, which showed clinically acceptable results for both the team and the patient.
- The results remained stable for 4 months with no relapse.

CONCLUSION

- Although many studies have used mesenchymal stem cells in clinics, data on using MSCs exosome therapy for GVHD are extremely limited. The experience of our team with hPMSC exosome-enriched EVs therapy on the described cutaneous cGVHD patient was clinically successful, making it a potential treatment for this pathology.
- However, further complementary studies and trials are strongly suggested.