Rheumatology International (2019) 39:933–941
https://doi.org/10.1007/s00296-019-04269-w

Rheumatology
INTERNATIONAL

CASE BASED REVIEW

Challenges in the diagnosis and treatment of disabling pansclerotic morphea of childhood: case-based review

Han Jie Soh[1] · Courtney Samuel[1] · Victoria Heaton[1] · William Douglas Renton[1] · Angela Cox[1] · Jane Munro[1,2]

Received: 10 January 2019 / Accepted: 28 February 2019 / Published online: 5 March 2019

Abstract

Disabling pansclerotic morphea of childhood (DPMC) is a rare subtype of juvenile localized scleroderma (JLS) characterized by pansclerosis mainly affecting children under the age of 14. This aggressive disease has a poor prognosis due to the rapid progression of deep musculoskeletal atrophy resulting in cutaneous ulceration and severe joint contractures. We describe the challenges in treating a previously well 5-year-old male who has refractory symptoms of DPMC. Over the 29 months, since his initial presentation, we trialed over ten therapies. There was subjective improvement with prednisolone and mycophenolate mofetil (MMF). However, other therapies including biologics and tyrosine kinase inhibitors (TKI) were ineffective. The patient has been referred for hematopoietic stem cell transplant given ongoing disease progression. We conducted a literature search focusing on English articles with keywords including DPMC. Publications with limited information or describing cases aged 20 and above were excluded. Thirty-seven case reports were identified and the reported treatments were evaluated. Methotrexate and corticosteroids have been the most commonly utilized. MMF has been anecdotally effective. Biologics, TKI, and Janus kinase inhibitors lack evidence in DPMC, but have had demonstrated efficacy in similar pathologies including systemic sclerosis, and, thus, have been used for DPMC. Phototherapy has been documented to be reducing skin thickness and stiffness of plaques. Eventually, most children require multi-modal and high-dose immunosuppressive therapies to reduce the inflammation inflicted by the disease. Long-term antibiotics and nutritional support are important in the ongoing care of these patients.

Keywords Disabling pansclerotic morphea of childhood · Pediatric · Children · Treatment

Introduction

Disabling pansclerotic morphea of childhood (DPMC) is a rare subtype of juvenile localized scleroderma (JLS) characterized by the rapid progression of deep cutaneous fibrosis or pansclerosis that involves the subcutaneous adipose tissue and, occasionally, the fascia, muscles, and bone [1, 2]. It was detailed in 1980 [2] and mainly affects children under the age of 14 [3]. Initially, the extremities would be involved and the disease would spread to the trunk, face, and scalp, while distal areas are spared [2]. DPMC is aggressive and prognosis is usually poor [1]. Complications include severe joint contractures, limb discrepancy, articular ankyloses [4, 5], and cutaneous ulceration which often results in septicemia [6]. Apart from marked functional and psychological impacts, neoplasia, cardiomyopathy, and restrictive pulmonary disease have also been reported [1, 4, 7–9]. The etiology is still

✉ Han Jie Soh
hanjie.soh@gmail.com

Courtney Samuel
dr.courtney.samuel@gmail.com

Victoria Heaton
tori.heaton@rch.org.au

William Douglas Renton
wdrenton@gmail.com

Angela Cox
angela.cox@rch.org.au

Jane Munro
jane.munro@rch.org.au

[1] Paediatric Rheumatology Unit, The Royal Children's Hospital, Parkville, VIC, Australia

[2] Arthritis and Rheumatology, Murdoch Children's Research Institute, Parkville, VIC, Australia

unknown, although vascular damage, increased collagen synthesis, and deposition along with altered B- and T-cell production and function may contribute to the cause [5]. Laboratory findings are non-specific. The most consistent findings from the previous studies were hypergammaglobulinemia and peripheral eosinophilia [2, 4, 10], although hypogammaglobulinemia has also been reported [11]. Cytokines including interleukin-6 (IL-6) have been suggested to play an integral role [12]. Antinuclear antibody (ANA) positivity has been reported in some cases [1, 13]. The values for cryoglobulins, rheumatoid factor, and complements are generally within normal ranges [2]. Histological findings have shown inflammatory round cell infiltrates to various depths, but the blood vessels are usually unaffected [2]. Due to the pansclerotic characteristics of DPMC, an excisional biopsy is recommended over the usual punch or incisional biopsy to evaluate the degree of inflammation [2].

Optimal treatment for DPMC is unknown and numerous treatments have been trialed in small numbers of patients with the mixed results. Methotrexate (MTX) [14], which is the first line for JLS [14–16], is frequently used for DPMC. Corticosteroids [4, 5, 17], mycophenolate mofetil (MMF) [12, 18], and tocilizumab [12] have also been used with some success [19]. Other therapies such as phosphodiesterase inhibitors, endothelin receptor antagonists, vitamin D analogues, antimalarials, D-penicillamine, colchicine, and topical psoralen with ultraviolet (UV) light treatment have been trailed with limited benefit [1, 4, 6, 13, 20–22]. Autologous stem cell transplantation appears to slow the progress of new lesions, but is not curative [23]. Most treatments described have varied efficacies. We aim to describe the challenges in treating a refractory patient with DPMC and to present a focused review of the literature of the therapeutic options that have been previously trialed.

Search strategy

We performed a literature search from January 1980 to June 2018 in PubMed, MEDLINE, EMBASE, Scopus, and Web of Science with keywords 'paediatric/pediatric', 'disabling pansclerotic morphea of childhood', 'treatment', and 'management'. Due to the various nomenclatures that have been previously used to describe DPMC, we streamlined our search to focus on articles that include DPMC as keywords. We included original articles, letters to the editor, and case reports published in English. Publications containing abstracts with limited information, comments, or involving case presentations of aged 20 and above were excluded. We identified 37 case reports and summarized the findings in Table 1.

Case presentation

A 5-year-old Caucasian male, who was previously well, presented with a 6-month history of generalized pain in most of his joints, morning stiffness, weight loss, and fatigue. He had been developmentally appropriate, was up-to-date with vaccinations, and had no significant family history. On examination, he had generalized tenderness and had proximal lower limb and truncal weakness. His skin over his proximal interphalangeal and metacarpophalangeal joints was tight and shiny. Mild desquamation and subtle patches of hypopigmentation and hyperpigmentation were noticed around his shoulders. Both his knees and wrists had active synovitis. He had mild generalized lymphadenopathy and mild hepatosplenomegaly.

The initial laboratory investigations are summarized in Table 2. His chest X-ray and electrocardiogram were both normal. Bone marrow analysis showed normal tri-lineage hematopoiesis with some reactive eosinophils and plasma cells. The initial magnetic resonance imaging (MRI) of his pelvis and lower limbs showed the evidence of extensive edema confined to the subcutaneous tissues, joint effusions throughout his joints, and bilateral inguinal lymphadenopathy. There was no evidence of myositis on MRI; however, Mi-2-alpha myositis-specific antibodies were weakly positive on immunofluorescence (but became negative on subsequent testing). Muscle enzymes activities were within normal range. Single-nucleotide polymorphism (SNP) array revealed a single long continuous stretch of homozygosity (5.9 Mb) detected on chromosome 7 of unknown significance.

Our patient was commenced on regular naproxen, prednisolone (1 mg/kg/day), and MTX (15 mg/m^2/week) for a presumed mixed connective tissue disease with the features of juvenile idiopathic arthritis, dermatomyositis, and localized scleroderma.

Three months after the initial presentation, his synovitis had resolved and his strength improved on these therapies. However, he still had progressive skin changes culminating in dyspigmentation and further sclerosis. He also started to develop lipodystrophy of the lower limbs. Monthly intravenous immunoglobulin (IVIG) (1 g/kg/month) and monthly methylprednisolone pulses (30 mg/kg/month) were added to the existing treatments. At 7 months, hydroxychloroquine (200 mg/dose 3 days a week) was added due to his cutaneous changes and incomplete response.

Due to progressing disease, a skin punch biopsy was performed 11 months into treatment. This showed hyperkeratosis with epidermal atrophy and diffuse dermal sclerosis consistent with scleroderma. A follow-up MRI of his whole body showed resolution of the previous diffuse subcutaneous edema and synovitis, although small effusions

Table 1 Reported cases of disabling pansclerotic morphea of childhood

First author	Year	Number of patients (*n*)	Gender	Age (years)	Treatment	Outcome	References
Diaz-Perez	1980	14	10 F; 4 M	1–14	Corticosteroids, cyclophosphamide, D-penicillamine, anti-malarial agents	2 (D); 9 (PD); 2 (PR)	[2]
Scharfetter-Kochanek	1995	1	1 F	8	PUVA	PR	[20]
Gruss	1997	1	1 M	16	UVA	PR	[38]
					Corticosteroids, cyclosporine	PD	
Todd	1998	1	1 F	7	PUVA, antibiotics, D-penicillamine, clobetasol	PD	[21]
Wollina	1998	1	1 M	11	IVIG	PR	[10]
					Antibiotics, nutritional supplements	PD	
Wollina	1999	1	1 M	12	Corticosteroids, PUVA bath therapy, ACEi	PR	[7]
					IVIG, antibiotics, pentoxifylline	PD	
Nguyen	2002	1	1 F	9	Arthrodesis	Stabilization of ankle	[28]
					Corticosteroids, MTX, D-penicillamine, corticosteroid injections	PD	
Wollina	2002	1	1 M	16	Acitretin, sterile maggots	D due to malignancy	[8]
Devidayal	2002	1	1 F	1.5	Antibiotics	D due to sepsis	[11]
Doede	2003	1	1 M	16	Antibiotics, PUVA bath therapy, sterile maggots	D due to malignancy	[36]
Yildrim	2003	1	1 F	8	UVA	PR	[13]
Roldan	2006	1	1 F	4	PUVA, bosentan	PR	[6]
					Corticosteroids, MTX, D-penicillamine, CCB, ACEi, Topical antiseptic therapy	PD	
Iqbal	2007	1	1 F	9	Corticosteroids	PD	[22]
Wollina	2007	3	1 M	17	IVIG, sildenafil	PR	[17]
					Corticosteroids, MTX, cyclosporine, D-penicillamine, nutritional supplements	PD	
			1 F	19	Corticosteroids, D-penicillamine, azathioprine, radiation therapy	PD	
			1 M	16	Corticosteroids, PUVA bath therapy, antibiotics, pentoxifylline, IVIG, ACEi	PR	
Forsea	2008	1	1 F	19	Corticosteroids, MTX, pulse MP, UVA, antibiotics, colchicine, piascledine, pentoxifylline, anti-platelet agents, nutritional supplements	PR	[4]
Petrov	2009	1	1 F	19	Radiation therapy	PR	[9]
					Corticosteroids, D-penicillamine, cyclophosphamide, azathioprine	PD	
Kura	2013	1	1 F	7	MTX, Pulse MP, PUVA, anticoagulants, anti-platelet agents	D due to sepsis	[5]
Odhav	2014	1	1 M	4	Corticosteroids, MTX, IV MP, MMF, IVIG, imatinib, abatacept	PR	[18]
					Autologous stem cell transplant	PR	
Dasgupta	2014	1	1 M	8	Corticosteroids, phenytoin, nutritional supplements	PD	[3]
Martini	2017	2	1 F	16	Corticosteroids, MTX, pulse MP, MMF, tocilizumab	PR	[12]
					Imatinib	PD	
			1 M	4	Corticosteroids, MTX, MMF, tocilizumab	PR	
					Pulse MP	PD	
Jamalpur	2018	1	1 F	15	Corticosteroids, MTX	PR	[27]

M male, *F* female, *UVA* ultraviolet A, *PUVA* Psoralen plus UVA, *IV* intravenous, *IVIG* IV immunoglobulin, *MP* methylprednisolone, *MMF* mycophenolate mofetil, *MTX* methotrexate, *CCB* calcium channel blocker, *ACEi* angiotensin-converting enzyme inhibitor, *D* death, *PD* progressive disease, *PR* partial response

Table 2 Initial laboratory results of the presented patient who was subsequently diagnosed with disabling pansclerotic morphea of childhood

Laboratory value	Results	Units	Reference ranges
Hemoglobin	118	g/L	110–140
White cell count	11.2	$\times 10^9$/L	6–17
Platelets	304	$\times 10^9$/L	150–400
C-reactive protein	< 5	mg/L	< 8
Erythrocyte sedimentation rate	7	mm/h	0–6
Aspartate aminotransferase level	149	IU/L	10–45
Alanine transaminase level	111	IU/L	5–45
Lactate dehydrogenase	1017	U/L	313–618
Creatinine kinase	141	IU/L	40–240
Ferritin	60	ug/L	8–160
Anti-nuclear antibody	1:320 (speckled)	–	–
Extractable nuclear antigen antibody	Negative	–	–
Anti-double-stranded DNA	Negative	–	–
Anti-phospholipid antibodies	Negative	–	–
Anti-neutrophil cytoplasmic antibody	Negative	–	–
Rheumatoid factor	Negative	–	–
Complement C3	1.21	g/L	0.70–2.06
Complement C4	0.25	g/L	0.11–0.61
Myositis antibody panel (Mi-2-alpha)	Positive	–	–
Fecal calprotectin	45	µg/g	< 150
Immunoglobulin G	9.6	g/L	5.28–21.90
Immunoglobulin A	0.46	g/L	0.61–3.45
Immunoglobulin M	0.61	g/L	0.48–2.26

were still noted in his left knee and ankle. Following these results, MMF (300 mg/dose, two times a day) was added. IVIG and the methylprednisolone pulses were ceased as his strength was now normal with no clinical or radiographic evidence of myositis. At this time, there was ongoing diagnostic uncertainty and clinical exome sequencing was arranged to investigate potential genetic causes.

Progressive distal digit lichenification and truncal hyperpigmentation ensued over the next few months. Methotrexate was, thus, recommenced, but, despite multiple immunosuppressive therapies, he developed further cutaneous changes, now affecting his face with ectropion. The lipodystrophy was progressing further and he started to develop contractures. Screening tests to investigate for the other organ involvement including echocardiogram and spirometry were normal. Fifteen months into treatment, rituximab was added. With the evolution of his symptoms, a diagnosis of disabling pansclerotic morphea of childhood was made. Tocilizumab was added 23 months into treatment on the recommendation of international expert consensus.

Despite the intensity of the treatment, the patient developed further cutaneous ulceration and infections and required multiple courses of antibiotics. In an attempt to reduce the ulceration and risk of sepsis, both bosentan at 62.5 mg twice daily and cotrimoxazole prophylaxis were commenced.

Over the next 3 months, there were extensive multidisciplinary discussions with oncologists, hematologists, and dermatologists, and it was determined that steroid-refractory graft versus host disease (GVHD) was the closest clinical entity to his histopathology sample. Thus, ruxolitinib, a Janus kinase inhibitor (JAKI), was suggested as per similar case reports [24, 25]. Tocilizumab was ceased and our patient commenced ruxolitinib for 3 months with minimal response.

Given the refractory nature of the disease course and lack of other therapeutic options, the patient has been referred for autologous hematopoietic stem cell transplant (HSCT) with CD34+ selection for his bone marrow graft. Twenty-nine months into treatment, our patient is on regular monthly methylprednisolone pulses (30 mg/kg/month), monthly IVIG (1 g/kg/month), oral prednisolone (10 mg/dose daily), MMF (400 mg/dose two times a day), naproxen (7.5 mg/kg/dose two times a day), and ruxolitinib (10 mg/dose two times a day). The progression of his disease can be noted in his clinical photos from Figs. 1 and 2. His key medications have been summarized in Fig. 3.

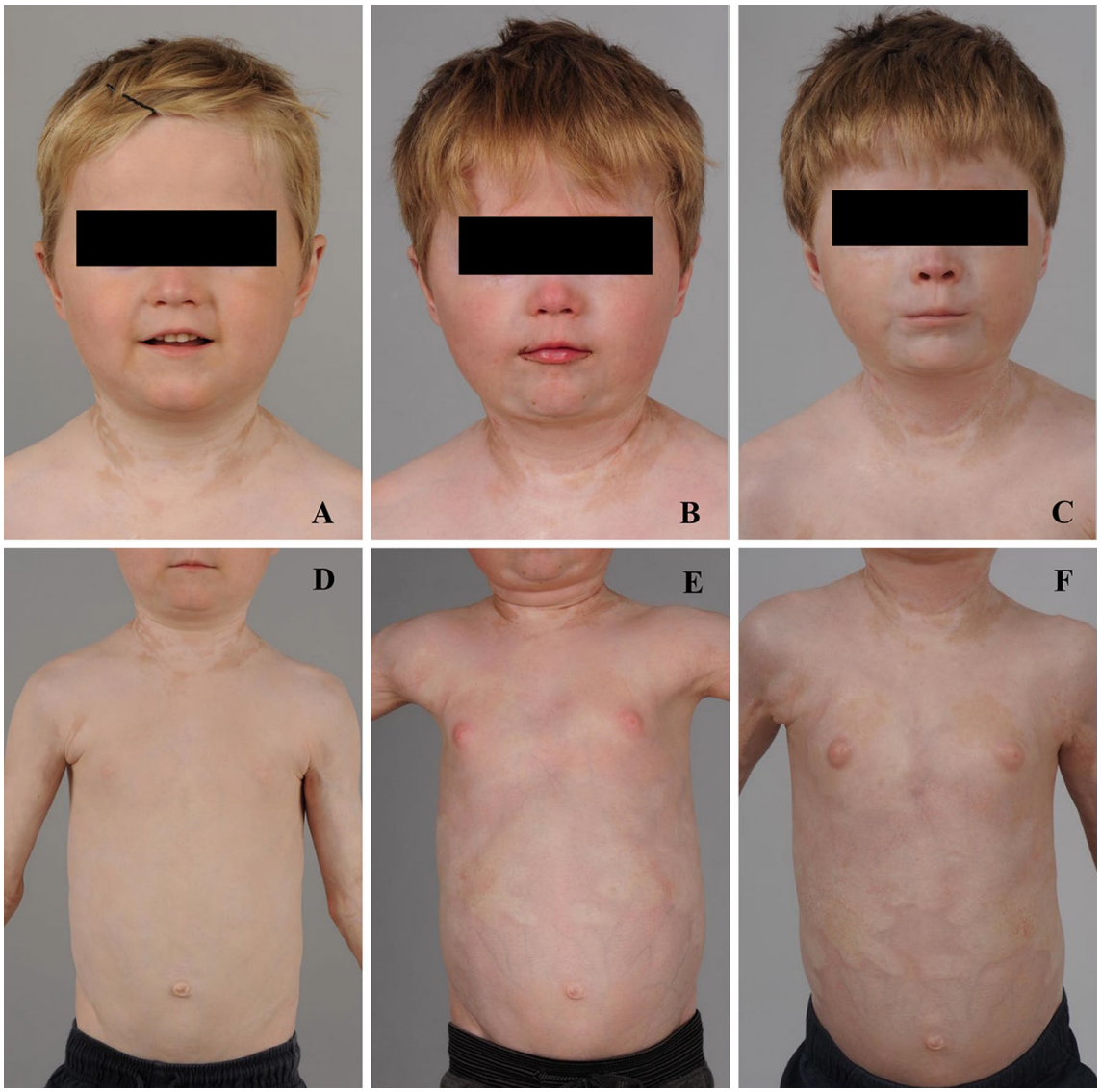

Fig. 1 Clinical photos of the presented patient's face and chest taken at various months into treatment for disabling pansclerotic morphea of childhood. **a, d** 13 months; **b, e** 21 months; **c, f** 28 months

Discussion

Our patient failed multiple therapies demonstrating the refractory and progressive nature of this rare condition. As there are no validated assessments for DPMC [26], we relied on subjective measures and clinical photography to note our patient's progress. With the limited evidence in the literature, it is interesting to note that the modified Rodnan Skin Score (mRSS) and the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) have been used by some authors to track patient's progress [12, 26]. Unfortunately, we have not used a clinical scoring system to monitor the progress of our patient.

Our patient trialed a combination of over ten therapies, but only had subjective improvements with prednisolone and MMF. Due to the lack of evidence, the treatment of DPMC is challenging. In a cross-sectional study [26], MTX was found to be the second most common initiated treatment in DPMC, after systemic corticosteroids. MTX is reported to disrupt the inflammatory cascade initiated by IL-1, IL-2, IL-4, IL-6, and tumor necrosis factor (TNF) [14]. This results in improvements in cutaneous sclerosis, which is thought to be caused by high serum levels of IL-2, IL-4, and IL-6. Eight of the case studies identified have used MTX either in combination with intravenous corticosteroid (methylprednisolone) [5, 6], oral corticosteroid (prednisolone) [17, 27, 28], or both [4, 12, 18] with varied successes.

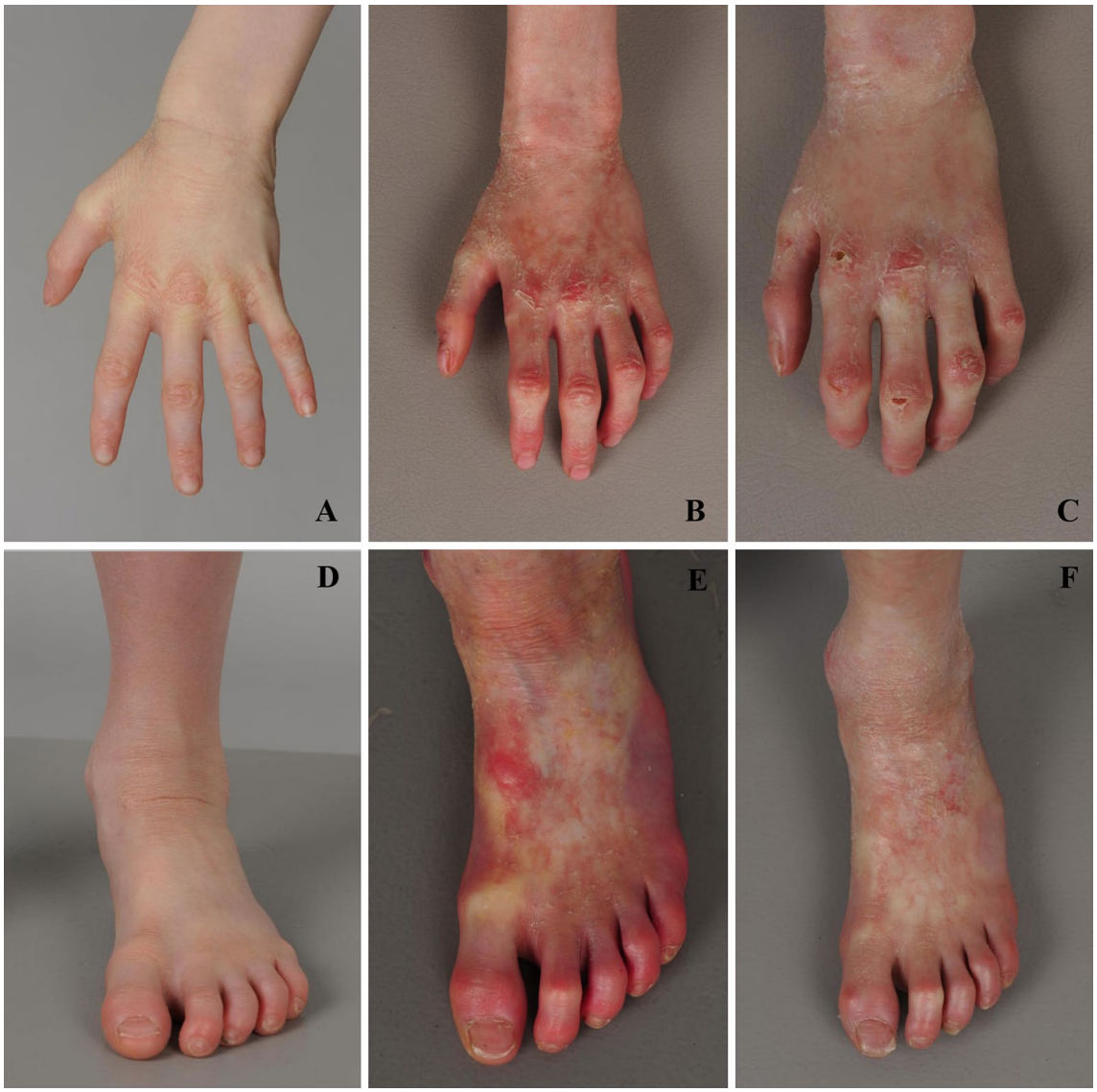

Fig. 2 Clinical photos of the presented patient's left hand and foot at various months into treatment for disabling pansclerotic morphea of childhood. **a** 7 months; **d** 4 months; **b, e** 21 months; **c, f** 28 months

Corticosteroids can be administered intravenously, orally, or topically. Of the four cases that had implemented pulse-therapy, two studies reported softening of the fibrosis and improved mobility of the involved joints [4, 12]. It must be recognized, however, that, in these cases, the treatment regimens included the other medications in addition to corticosteroids. The majority of the other case reports also included either regular oral or intravenous corticosteroids as part of their treatment regimen and reported varied improvements in their patients [2, 3, 7, 9–11]. However, none of the cases specifically reported the use of topical corticosteroids. Apart from MTX and corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) have been commonly used [2, 13]. Long-term antibiotics such as penicillin and nutritional supplements have also been part of the regimen in majority of the case reports to prevent possible clinical infection [3, 4, 9, 17, 21, 28]. In the event when ongoing infection occurs despite systemic antibiotics, several case reports have reported success with IVIG [7, 10, 18].

In recent years, other therapies that have been trialed to complement the initial treatments include MMF, biologics, tyrosine kinase inhibitors (TKI), and JAKI. Despite the lack in evidence, these treatments have demonstrated efficacy in similar pathologies including systemic sclerosis and, thus, have been used for DPMC [29–32]. MMF has been shown to have anti-fibrotic and immunosuppressive effects [31]. In the previous studies, it was shown to inhibit type 1 collagen expression, enhance the expression of matrix

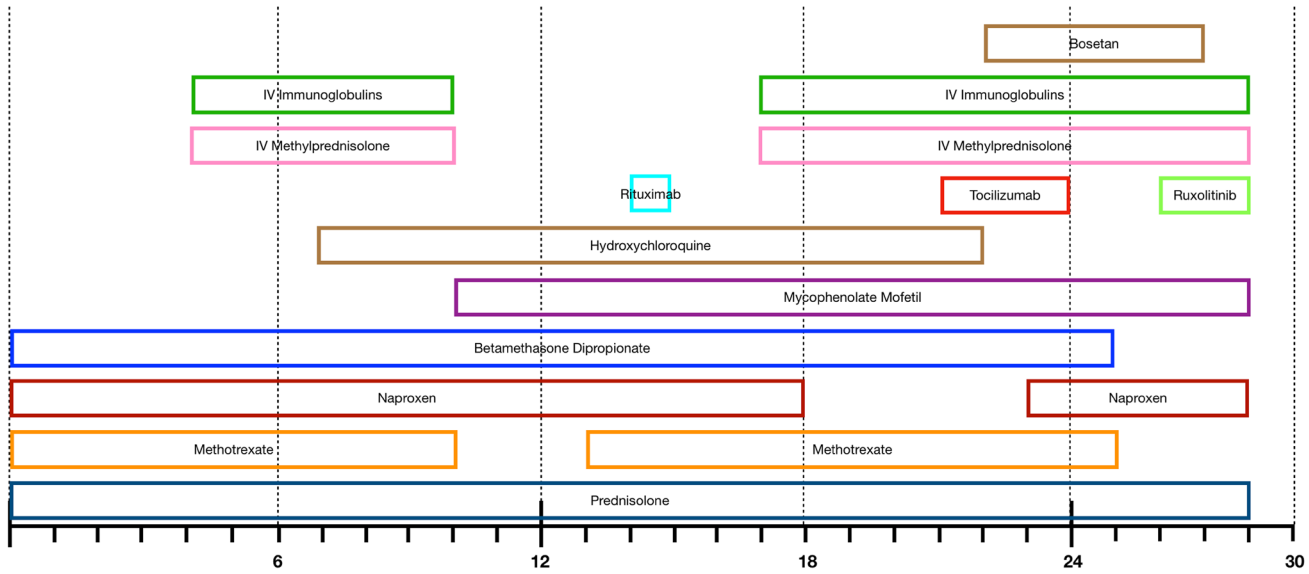

Fig. 3 The presented patient's key medications detailed up to 29 months into treatment for disabling pansclerotic morphea of childhood

metalloproteinase-1 (MMP-1), and alter the migratory and contractile function of fibroblasts [31]. Although MMF had been successful in our patient and has been anecdotally effective, there is limited evidence in the literature reporting the effectiveness of MMF in DPMC [16, 31]. In the case reports that we identified, only two prescribed MMF for their patients [12, 18], suggesting that this treatment may be underutilized in DPMC. Biologics are also currently underutilized due to the limited reported use. Tocilizumab is an anti-IL-6 receptor antibody and abatacept inhibits T-cell activation decreasing IL-2, IL-4, IL-6, and IL-17 expression [30]. Given that IL-6 plays an integral role in DPMC by regulating fibroblast differentiation and stimulating collagen synthesis [12], abatacept and tocilizumab are strong candidate drugs for managing DPMC. Martini et al. suggested that tocilizumab may be helpful to inhibit the progression of disease using a regimen of 8 mg/kg every 4 weeks [12], while Odhav et al. utilized abatacept and found improvement in skin lesions [18]. However, Odhav et al. did not describe the regimen [18]. With our case study, we trialed rituximab as it has been helpful in managing a variety of refractory pediatric autoimmune diseases [33]. Unfortunately, there was minimal response in our patient who was on the regimen of two doses of 500 mg/m^2 every 2 weeks for 3 months. With regards to TKI and JAKI, there had been varied responses. In one case report, there had been ongoing fibrosis with minimal improvements when imatinib was trialed [12]. However, Odhav et al. noticed an improvement skin discoloration and increased joint range of motion in his presented patient with imatinib [18]. With our patient, we had a poor response with ruxolitinib, although the current literature reports promising findings in adults [34].

In the early reports, phototherapy was frequently used. There are three basic subtypes; UVA (UVA1 and UVA2), UVB (broadband and narrowband), and UVC [35]. Most reports have focused on the use of bath-PUVA (topical psoralen and UVA exposure), which improves and clears fibrotic plaques in some cases [7, 17, 20, 36]. It avoids the side effects of oral psoralen such as necessity of eye protection in sunlight and nausea [37]. In some case studies, broadband UVA and UVA-1 was used to reduce skin thickness and stiffness of plaques [13, 38].

From the literature, several therapies have been proven effective in individual reports. This includes sildenafil [17], for ulcers due to its antitumoral effect in vitro, and bosentan [6], for possible treatment in vasculopathy in DPMC. Alternative options such as colchicine, cyclosporine, interferon gamma, tacrolimus, and recombinant human relaxin have been trialed based on the different backgrounds of patients [4]. Although these are not first-line treatments, they act as supportive therapies to reduce inflammation [27].

We conclude that most children with DPMC require multi-modal and high dose immunosuppressive therapy with the initial treatment regimens involving MTX and systemic corticosteroids. Our case study is a prime example that reflects the challenges in treating DPMC. We acknowledge that the small number of case studies and inconsistent treatment regimens limits our ability to note definitive trends of effective pharmacological interventions. The addition of further interventions for possible refractory cases would be dependent on the judgement of the treating clinician.

Perhaps, with the increasing case reports of DPMC and in the era of biologics, we will able to observe a promising trend in successful treatments.

Author contributions HJS wrote the initial draft of the manuscript and reviewed the literature. CS, VH, and WDR revised and contributed to the editing of manuscript, reviewed the literature, and managed the ongoing treatment of our patient. AC and JM critically revised the manuscript and managed the ongoing treatment of our patient.

Funding None.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethics approval This research has been approved by the Human Research Ethics Committee by The Royal Children's Hospital, Melbourne, Australia (HREC 38167).

Informed consent Informed consent was obtained from the parents of the presented patient for publication and for clinical photography to be used for research purposes.

References

1. Wollina U, Buslau M, Petrov I, Pramatarov K (2007) Disabling pansclerotic morphea of childhood. Expert Rev Dermatol 2:775–784
2. Diaz Perez JL, Connolly SM, Winkelmann RK (1980) Disabling pansclerotic morphea of children. Arch Dermatol 116:169–173
3. Dasgupta MK, Patra C, Sarkar S, Das S (2014) Pansclerotic morphea: a male child with hemiatrophy of lower limb. Indian Dermatol Online J 5:170–172
4. Forsea AM, Cretu AN, Ionescu R, Giurcaneanu C (2008) Disabling pansclerotic morphea of childhood—unusual case and management challenges. J Med Life 1:348–354
5. Kura M, Jindal S (2013) Disabling pansclerotic morphea of childhood with extracutaneous manifestations. Indian J Dermatol 58:159
6. Roldan R, Morote G, Castro MDC, Miranda MD, Moreno JC, Collantes E (2006) Efficacy of bosentan in treatment of unresponsive cutaneous ulceration in disabling pansclerotic morphea in children. J Rheumatol 33:2538–2540
7. Wollina U, Looks A, Uhlemann C, Wollina K (1999) Pansclerotic morphea of childhood-follow-up over 6 years. Pediatr Dermatol 16:245–247
8. Wollina U, Buslau M, Weyers W (2002) Squamous cell carcinoma in pansclerotic morphea of childhood. Pediatr Dermatol 19:151–154
9. Petrov I, Gantcheva M, Miteva L, Vassileva S, Pramatarov K (2009) Lower lip squamous cell carcinoma in disabling pansclerotic morphea of childhood. Pediatr Dermatol 26:59–61
10. Wollina U, Looks A, Schneider R, Maak B (1998) Disabling morphoea of childhood—beneficial effect of intravenous immunoglobulin therapy. Clin Exp Dermatol 23:292–293
11. Devidayal, Singh S, Kumar L, Radotra B (2002) Disabling pansclerotic morphea of childhood and hypogammaglobulinemia: a curious association. Rheumatol Int 21:158–160
12. Martini G, Campus S, Raffeiner B, Boscarol G, Meneghel A, Zulian F (2017) Tocilizumab in two children with pansclerotic morphoea: a hopeful therapy for refractory cases? Clin Exp Rheumatol Suppl 106:211–213
13. Yildirim M, Baysal V, Aridogan BC, Kesici D, Erturan I (2003) Pansclerotic morphea treated with UVA: a case report. J Dermatol 30:625–627
14. Zulian F, Martini G, Vallongo C, Vittadello F, Falcini F, Patrizi A, Alessio M, La Torre F, Podda RA, Gerloni V, Cutrone M, Belloni-Fortina A, Paradisi M, Martino S, Perilongo G (2011) Methotrexate treatment in juvenile localized scleroderma: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 63:1998–2006
15. Torok KS, Arkachaisri T (2012) Methotrexate and corticosteroids in the treatment of localized scleroderma: a standardized prospective longitudinal single-center study. J Rheumatol 39:286–294
16. Li SC, Torok KS, Pope E, Dedeoglu F, Hong S, Jacobe HT, Rabinovich CE, Laxer RM, Higgins GC, Ferguson PJ, Lasky A, Baszis K, Becker M, Campillo S, Cartwright V, Cidon M, Inman CJ, Jerath R, O'Neil KM, Vora S, Zeft A, Wallace CA, Ilowite NT, Fuhlbrigge RC (2012) Development of consensus treatment plans for juvenile localized scleroderma: a roadmap toward comparative effectiveness studies in juvenile localized scleroderma. Arthritis Care Res 64:1175–1185
17. Wollina U, Buslau M, Heinig B, Petrov I, Unger E, Kyriopoulou E, Koch A, Kostler E, Schonlebe J, Haroske G, Doede T, Pramatarov K (2007) Disabling pansclerotic morphea of childhood poses a high risk of chronic ulceration of the skin and squamous cell carcinoma. Int J Low Extremity Wounds 6:291–298
18. Odhav A, Hoeltzel MF, Canty K (2014) Pansclerotic morphea with features of eosinophilic fasciitis: distinct entities or part of a continuum? Pediatr Dermatol 31:e42–e47
19. Li SC, Feldman BM, Higgins GC, Haines KA, Punaro MG, O'Neil KM (2010) Treatment of pediatric localized scleroderma: results of a survey of North American pediatric rheumatologists. J Rheumatol 37:175–181
20. Scharffetter-Kochanek K, Goldermann R, Lehmann P, Holzle E, Goerz G (1995) PUVA therapy in disabling pansclerotic morphoea of children. Br J Dermatol 132:830–831
21. Todd DJ, Askari A, Ektaish F (1998) PUVA therapy for disabling pansclerotic morphoea of children. Br J Dermatol 138:201–202
22. Iqbal MP, Bajaj DR (2007) Disabling pansclerotic and plaque morphoea. J Coll Phys Surg Pak 17:495–496
23. Moll M, Holzer U, Zimmer C, Rieber N, Kuemmerle-Deschner JB (2011) Autologous stem cell transplantation in two children with disabling pansclerotic morphea. Pediatr Rheumatol Online J 9:P77
24. Kim SR, Charos A, Damsky W, Heald P, Girardi M, King BA (2018) Treatment of generalized deep morphea and eosinophilic fasciitis with the Janus kinase inhibitor tofacitinib. JAAD Case Rep 4:443–445
25. Hurabielle C, Sicre de Fontbrune F, Moins-Teisserenc H, Robin M, Jachiet M, Coman T, Dhedin N, Cassius C, Chasset F, De Masson A, Michonneau D, Bagot M, Bergeron A, Socie G, Peffault De Latour R, Bouaziz JD (2017) Efficacy and tolerance of ruxolitinib in refractory sclerodermatous chronic graft-versus-host disease. Br J Dermatol 177:e206–e208
26. Kim A, Marinkovich N, Vasquez R, Jacobe HT (2014) Clinical features of patients with morphea and the pansclerotic subtype: a cross-sectional study from the morphea in adults and children cohort. J Rheumatol 41:106–112
27. Jamalpur I, Mogili HR, Koratala A (2018) Disabling pansclerotic morphoea of childhood. BMJ Case Rep. https://doi.org/10.1136/bcr-2017-222132
28. Nguyen XH, Hansen R, Valencia F (2002) Severe ankle deformity secondary to pansclerotic morphea in a 9-year-old girl: correction

involving arthrodesis and free flap coverage. Pediatr Dermatol 19:560–563
29. Iwamoto N, Distler JHW, Distler O (2011) Tyrosine kinase inhibitors in the treatment of systemic sclerosis: from animal models to clinical trials. Curr Rheumatol Rep 13:21–27
30. Bruni C, Praino E, Allanore Y, Distler O, Gabrielli A, Iannone F, Matucci-Cerinic M (2017) Use of biologics and other novel therapies for the treatment of systemic sclerosis. Expert Rev Clin Immunol 13:469–482
31. Martini G, Ramanan AV, Falcini F, Girschick H, Goldsmith DP, Zulian F (2009) Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. Rheumatology 48:1410–1413
32. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A (2013) Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis 72:ii111–ii1115
33. Tzaribachev N, Koetter I, Kuemmerle-Deschner JB, Schedel J (2009) Rituximab for the treatment of refractory pediatric autoimmune diseases: a case series. Cases J 6:6609
34. MacDonald KPA, Betts BC, Couriel D (2018) Emerging therapeutics for the control of chronic graft-versus-host disease. Biol Blood Marrow Transplant 24:19–26
35. Narbutt J, Hołdrowicz A, Lesiak A (2017) Morphea—selected local treatment methods and their effectiveness. Reumatol/Rheumatol 55:305–313
36. Doede T, Wollina U, Hindermann W, Schier F, Bondartschuk M (2003) Pansclerotic morphea in childhood: a case report. Pediatr Surg Int 19:406–408
37. Sunderkötter C, Kuhn A, Hunzelmann N, Beissert S (2006) Phototherapy: a promising treatment option for skin sclerosis in scleroderma? Rheumatology 45:iii52–iii54
38. Gruss C, Stucker M, Von Kobyletzki G, Schreiber D, Altmeyer P, Kerscher M (1997) Low dose UVA1 phototherapy in disabling pansclerotic morphoea of childhood. Br J Dermatol 136:293–294