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Case Series

Dermatology Section

Localised Morphea Treated Empirically with Ceftriaxone

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ABSTRACT

Localised morphea is an autoimmune sclerosing disorder of unknown aetiology. Various triggering factors are known to be associated with the disease including infections, vaccination, autoimmune disorders, and trauma. Amongst the infections, the common causative organisms associated with morphea are Borrelia burgdorferi, varicella, and Epstein-Barr virus (EBV). Localised morphea presents as an initial inflammatory stage and a late inactive stage. It is characterised by sclerosis of skin with hyper or depigmentation. The antibiotics effective against borrelia infection are benzyl penicillin, doxycycline, and ceftriaxone. These antibiotics are tried in the treatment of localised morphea. Ceftriaxone is one of the best antibiotics preferred to treat borrelia infection at all stages. Apart from its antibiotic properties, it also has an anti-inflammatory and collagen remodelling properties. All five cases of localised morphea reported here were biopsy proven, Antinuclear Antibody (ANA) and Rheumatoid Arthritis (RA) factor negative. All the cases were treated with weekly single intramuscular dose of ceftriaxone 250 mg. After eight weeks there was remarkable improvement in the induration and pigmentation of the lesions.

Keywords: Antibiotics, Infection, Scleroderma

INTRODUCTION

Morphea, commonly known as localised scleroderma is a fibrosing autoimmune disorder. Though not rare, its incidence is 0.4-2.7 per 1,00,000 people [1]. There is a female preponderance of 2 to 4.2:1 globally [2]. Localised morphea affects all races but seen more commonly in whites [1]. Its peak incidence occurs in fifth decade of life and 2-14 years in children [1]. Various triggering factors proposed in the pathogenesis of morphoea include infections (EBV, cytomegalovirus, Borrelia burgdorferi), local trauma, radiation, drugs, vaccinations and microchimerism [1,2]. It is proposed that the initial event in the pathogenesis of morphea is the vascular injury in a genetically susceptible host, which in turn initiates an autoimmune process and then abnormal fibrosis [2,3]. The prognosis of localised scleroderma is good when only superficial involvement is there. The involvement of deeper structures such as subcutaneous fat, muscle, fascia, and bone can cause disability and disfigurement. The authors here are presenting a case series of localised morphea with good response to empirical ceftriaxone therapy.

CASE SERIES

Case 1

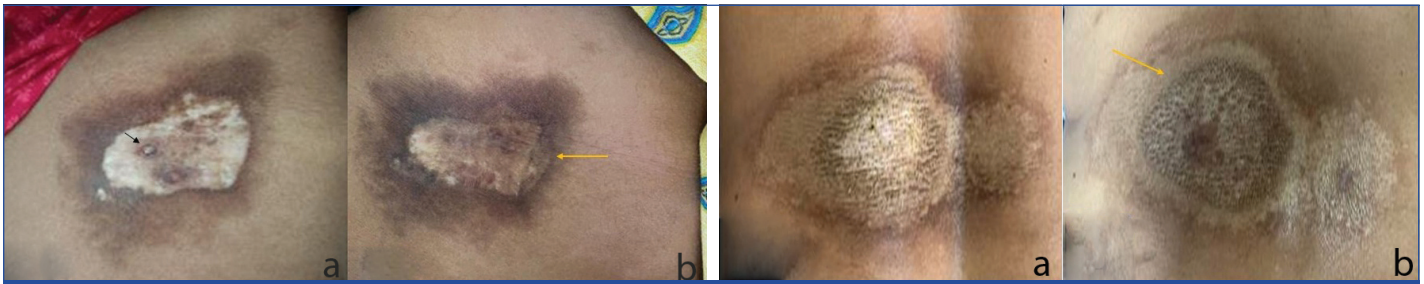
A 32-year-old female complained of asymptomatic skin lesion on the right-side of abdomen which was gradually increasing in size and thickness since four months. There was no history of joint pain, Raynaud's phenomenon, oral ulcers, or weight loss. On examination, there was a solitary indurated plaque measuring 8×5 cm with depigmentation and surrounding hyperpigmentation on the right upper quadrant of abdomen [Table/Fig-1] giving an "owl's eye appearance". On palpation, there was no deep tenderness. Skin biopsy revealed epidermal atrophy with loss of rete ridges and upper dermis showed dense collagen deposits with loss of adnexal structures suggestive of morphea.

Case 2

A 35-year-old female noticed skin lesion on the trunk since six months. The lesion was initially small gradually increasing to reach present size of 10×6 cm on right-side of the trunk. The patient did not give any history of joint pain, oral ulcers, weight loss or photosensitivity. On examination, there was an indurated depigmented plaque with peripheral rim of pigmentation [Table/Fig-2] giving an "owl's eye appearance". Skin biopsy showed epidermal atrophy with dense dermal collagen deposits and loss of adnexal structures.

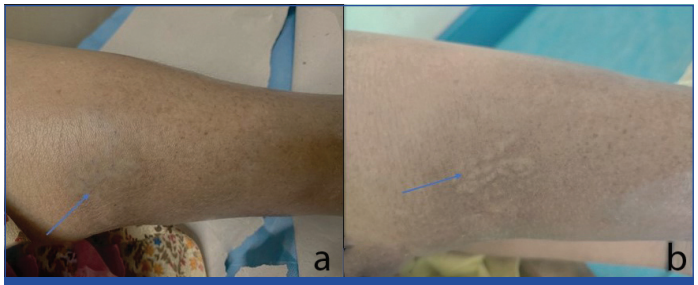
Case 3

A 65-year-old female with complaints of painful thickening of skin on the right lower limb since two months. She was a known diabetic on oral hypoglycaemic drugs. On examination, there was an indurated plaque with hyperpigmentation on the posterior aspect of right foreleg [Table/Fig-3]. The surface showed a few linear areas of



[Table/Fig-1]: Case 1 (a) Before treatment: Depigmented indurated plaque (black arrow) with surrounding area of hyperpigmentation; (b) After treatment: Showing significant improvement with repigmentation of the plaque and decreased induration (yellow arrow). **[Table/Fig-2]:** Case 2 (a) Before treatment: Indurated plaque with specks of pigmentation in the centre; (b) After treatment: Marked reduction in induration and size of the lesion after treatment. (Images from left to right)

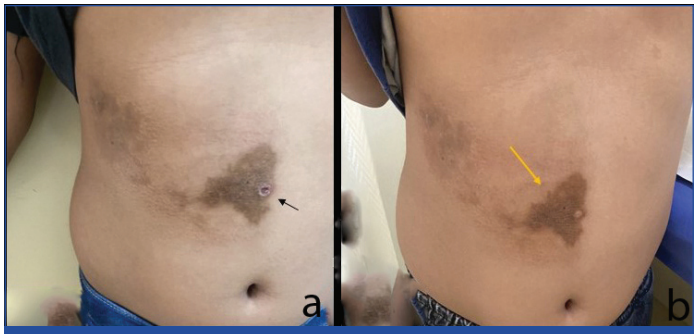
ivory colour plaque. On palpation, there was sclerosis with deep tenderness. Skin biopsy showed epidermis normal, dermis showed denatured collagen extending up to subcutaneous tissue. There were reduced appendageal structures with inflammatory infiltrate.



[Table/Fig-3]: Case 3 (a) Before treatment: An indurated plaque with ivory white streaks of sclerosis (blue arrow) present on the right foreleg; (b) After treatment: Reduced induration with linear areas of scarring after treatment (blue arrow).

Case 4

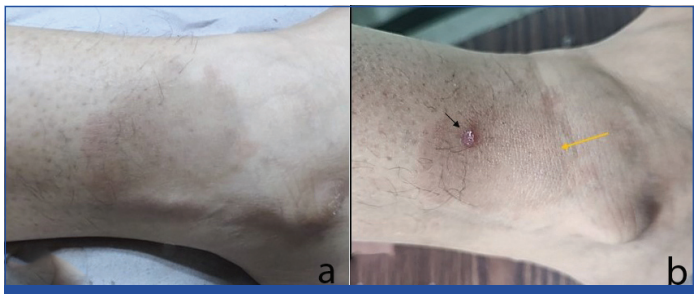
A five-year-old boy gives history of asymptomatic dark coloured skin lesion over the anterior abdomen since two years, which was initially coin sized and then slowly progressed in size. On examination, there was a well-defined hyperpigmented plaque of size 5×7 cm present, 4 cm above umbilicus with a shiny surface [Table/Fig-4]. On palpation there was induration without tenderness. Similar small hyperpigmented plaques were present in a linear pattern on right-side of the abdomen. Skin biopsy showed flattened epidermis with loss of rete ridges and dermis showed loss of skin appendages amidst thick collagen bundles with perivascular lymphocytes and a few plasma cells.



[Table/Fig-4]: Case 4 (a) Before treatment: Hyperpigmented indurated plaque present over the right-side of the abdomen; (b) After treatment: yellow arrow highlighting marked improvement in the induration and decrease in the intensity of pigmentation.

Case 5

A 42-year-old female visited Dermatology Outpatient Department (OPD) as she noticed an asymptomatic plaque on the right foot since two months. There was a history of insect bite three months back at the same site. The lesion was initially small and pigmented and it gradually increased in size over a period of three weeks. On examination, there was a hyperpigmented plaque with induration and erythematous border on lateral aspect of right leg [Table/Fig-5]. Skin biopsy showed atrophic epidermis and thickened dermis with sclerotic collagen extending into the subcutis, atrophy of adnexal structures with mild perivascular infiltrate, suggestive of morphea.



[Table/Fig-5]: Case 5 (a) Before treatment: Hyperpigmented sclerosed plaque with erythematous borders; (b) After treatment: Reduced induration and pigmentation with faint erythema (yellow arrow).

Routine blood tests done in all the cases were normal and ANA immunofluorescence was negative in all the cases. Initial assessment of the severity of lesions was made by Localised Scleroderma Cutaneous Assessment Tool (LoSCAT) score with respect to pigmentation and induration [4]. The ceftriaxone injections (intramuscular) given to all the cases was around 4 mg/kg/dose/week for 8 weeks. During the treatment, no adverse effects were observed in all the cases except for mild pain at the injection site. After 8 weeks, the lesions which were depigmented initially gained pigmentation gradually [Table/Fig-1b,2b] and hyperpigmented lesions showed decrease in pigmentation [Table/Fig-4b,5b] both suggesting healing process as they were all associated with reduction in induration. In case 3, as there was subcutaneous involvement of sclerosis, the linear ivory white plaques healed with linear atrophic scar and reduced induration of the surrounding skin [Table/Fig-3b]. The improvement of lesions in terms of induration and pigmentation was assessed by LoSCAT scoring after 8 weeks of treatment. All the cases showed a reduction in LoSCAT score ranging from 4-8 (before treatment) to 0-4 (after treatment). The details of the lesions before and after treatment are mentioned in the [Table/Fig-6].

DISCUSSION

Morphea is a chronic fibrosing disorder of unknown aetiology involving the skin and underlying tissues such as subcutaneous tissue, fascia, muscle, and bone [2]. It can be localised or generalised. Among the localised type, plaque type of morphea is more common in adults and linear variety is mostly prevalent in children [1,2]. It is postulated that around 2-5% of localised childhood morphea are associated with autoimmune diseases [1]. Around 20-80% of morphea patients have positive serological test of autoimmunity [1]. In the case series presented here, all of them had negative ANA immunofluorescence and RA factor. Zinchuk

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	32	35	65	5	42
Sex	Female	Female	Female	Male	Female
Location of the lesion	Right upper quadrant of abdomen.	Left side of mid trunk.	Posterior aspect of right foreleg.	Right upper quadrant of abdomen.	Lower lateral aspect of right foreleg above lateral malleolus.
Ceftriaxone (dose for 8 weeks)	250 mg/week	250 mg/week	250 mg/week	125 mg/week	250 mg/week
LoSCAT (before treatment)					
LoSAI[#]	5	6	6	5	5
LoSDI[$]	5	5	6	8	4
LoSCAT (after treatment)					
LoSAI	1	1	1	4	0
LoSDI	2	2	2	4	1

[Table/Fig-6]: Details of the lesions before and after treatment in all the five cases.
*LoSCAT: Localised scleroderma cutaneous assessment tool; #LoSAI: Localised scleroderma activity index; $LoSDI: localised scleroderma damage index

AN et al., studied 32 cases of localised scleroderma patients and they found around 18.8% showed positive serology for antiborrelia antibodies indicating the possible role of Borrelia burgdorferi as the triggering factor [5]. Aberer E et al., found that among 15 patients who had tick bite, four of them developed morphea [6]. Here, only case 5 gave a history of insect bite before the lesion appeared. As there is negative autoimmune serology in all these cases, suspecting the infective aetiology in localised morphea, an empirical treatment with ceftriaxone has been tried in these patients.

Localised morphea presents with an early inflammatory stage and a late inactive stage. In the inflammatory stage, there is erythematous to violaceous patch or plaque which later forms white sclerotic plaque in the centre with surrounding postinflammatory hyperpigmentation [1,2]. In some cases, due to excessive collagen deposition and fat trapping, there is destruction of appendages [1,2]. All the cases presented here had postinflammatory pigmentary changes except case 5 which showed surrounding erythematous border.

In 1985, Aberer E et al., proposed a hypothesis that morphea is caused by infection due to borrelia due to similar clinical and histological features between morphea and acrodermatitis chronica atrophicans [7]. They also found that there was 50% serological positivity to borrelia Infections in their morphea patients [7]. There are a few case reports on association or co-existence of skin lesions due to borrelia infection and morphea [3,8]. Weide B et al., in their review on association of borrelia infection and morphea, proposed that antibiotic therapy against borrelia infection in morphea helps in halting the disease progression [8]. Detection of borrelia organism in tissue samples of morphea by polymerase chain reaction has also been done in several parts of the world with controversial results in delineating the possible association of borrelia infection and localised morphea [8]. Aberer E et al., in their in-vitro study showed that certain strains of borrelia species prevalent in Europe and Asia can trigger skin fibrosis by stimulating profibrotic molecules [9]. However, there are a few case reports of localised morphea which are treated with antibiotics such as benzyl penicillin and ceftriaxone with good response, even in absence of borrelia antibodies detection [5,10,11]. It is said that detection of antibodies against borrelia in blood is difficult as it escapes the humoral immune response in morphea, hence polymerase chain reaction is the most confirmatory test for detection of presence of organism [8]. Due to lack of laboratory facility, antiborrelia antibodies assay was not performed in any of the index cases.

There are various treatment modalities for localised morphea-topical steroids, calcipotriol, phototherapy, methotrexate, and mycophenolate mofetil. All these modalities help in reducing the inflammation and the progression of disease [1,2]. Previously, it was suggested that the advantage of benzyl penicillin in the treatment of localised scleroderma is due to its antibiotic property against borrelia infection and its metabolite penicillamine inhibiting insoluble collagen formation [5]. Ceftriaxone is one of the best antibiotics preferred to treat borrelia infection at all stages. Apart from its antibiotic properties, it also has an anti-inflammatory and collagen remodelling properties [12,13]. Feng J et al., found in their in-vitro study that ceftriaxone pulse dosing is effective to eliminate log phase of borrelia burgdorferi persisters. The pulse dosing treatment helps to allow non growing antibiotic tolerant persisters formed after drug treatment to recover and become growing spirochetes, so they become susceptible to drugs again [12]. All the five cases responded very well clinically with ceftriaxone antibiotic treatment.

CONCLUSION(S)

The authors conclude that in localised scleroderma, an empirical treatment of ceftriaxone can be tried in presence of negative autoimmune serological profile. Though localised morphea is self-limiting disease, the treatment with antibiotics against borrelia organism can help in halting the progression of the disease. Hence, all cases of localised morphea should undergo serological test for autoimmune work-up and antiborrelia antibodies. Though the association between borrelia and morphea is controversial, further studies need to be done in this aspect as per geographical location. The efficacy of empirical treatment of ceftriaxone in morphea needs to be validated by further studies.

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