

1 **Scleredema diabeticorum partially treated with low-dose methotrexate: A Report of five**
2 **cases**

3 **Short title:** Scleredema treated with low-dose methotrexate

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5 **Düşük doz metotreksate ile kısmen tedavi edilen skleredema diyabetorum: 5 olgu**
6 **sunumu**

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8 **Kısa başlık:** Skleredema tedavisinde düşük doz metotreksate

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26 **Scleredema diabeticorum partially treated with low-dose methotrexate: A Report of five**
27 **cases**

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29 **Abstract**

30 Scleredema is a rare connective tissue disorder that belongs to a group of scleroderma-like
31 disorders. Although there is not a known curative therapy exists, various specific treatments
32 proposed in the literature. In this report, we describe five cases of scleredema partially treated
33 with low-dose methotrexate therapy. All patients have diabetes mellitus type II. All patients
34 were started on methotrexate 15 mg subcutaneously once weekly for 3 months. Biopsy
35 specimens were taken from all patients and were examined histologically before the
36 treatment and after 3 months of treatment. All cases partially responded to low-dose
37 methotrexate therapy. We believe that methotrexate therapy may be an alternative therapeutic
38 options in scleredema in view of its efficacy.

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40 **Key words:** Scleredema, low-dose methotrexate, diabetes mellitus

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51 **Düşük doz metotreksate ile kısmen tedavi edilen skleredema diyabeticorum: 5 olgu**

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54 **Özet**

55 Skleredema nadir görülen skleroderma-benzeri bir grup konnektif doku hastalıklarından
56 biridir. Bilinen küratif bir tedavisi olmamakla birlikte literatürde birçok tedavi şekli
57 bildirilmiştir. Burada düşük-doz metotreksate tedavisine kısmen cevap veren 5 olgu
58 sunulmaktadır. Tüm hastalar aynı zamanda tip II diyabetes mellitus hastası idi. Tüm hastalara
59 3 ay süre ile subkutan yolla 15mg/hafta metotreksate tedavisi verildi. Tüm hastalaradan tedavi
60 öncesi ve tedavi sonrası biyopsi alınarak karşılaştırıldı. Tüm hastaların bu tedaviye kısmen
61 cevap verdiği histopatolojik olarak gösterildi. Sonuç olarak, düşük doz metotreksate tedavisi
62 skleredema için alternatif bir tedavi metodu olabilir.

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64 **Anahtar Kelimeler:** Skleredema, düşük doz metotreksate, diyabetes mellitus

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76 **Introduction**

77 Scleredema is a rare connective tissue disorder, with an unclear pathogenetic mechanism. It is
78 characterized by diffuse, nonpitting swelling and induration of the skin that typically begins at
79 the neck and spreads to the face, scalp, shoulders, and trunk. The hands and feet are
80 characteristically spared.^[1,2] Three types of scleredema are differentiated. Type 1 is usually
81 preceded by a febrile episode and resolves spontaneously. Type 2 is associated with
82 developing paraproteinemias including multiple myeloma. Type 3 is associated with diabetes
83 mellitus so-called scleredema diabetorum.^[2,3] Many therapies, including ultraviolet (UV)
84 A1 phototherapy, bath psoralen UVA, extracorporeal photopheresis, radiation, electron beam,
85 prostaglandin E1, cyclosporine and high-dose penicillin have been used with varying degree
86 of success in separate case reports.^[4,5] There are some conflicting data about treatment
87 success of low dose-methotrexate (MTX) regimen in scleredema in literature.^[6,7]

88 Herein we report five cases of scleredema. It is remarkable that all the cases have diagnosed
89 type II diabetes mellitus. All cases showed partial clinical and histopathological improvement
90 to low-dose MTX therapy without obvious side effects. We examined efficacy of low-dose
91 MTX treatment evaluating biopsy specimens histologically.

92 **Cases**

93 Case 1: A 40-year-old man presented with acneiform lesions on his posterior neck. His
94 medical history was unremarkable. On his dermatological examination in addition to some
95 acneiform papules on his neck, diffuse hardening of the skin of his posterior neck and upper
96 back was noticed (Figure 1). There was no involvement of the hands or lower extremities.
97 Patient was unaware of this abnormality. His laboratory evaluation revealed a blood glucose
98 level of 303 mg/dL and hemoglobin A1C level of 8.0%. A biopsy specimen from the skin of
99 his back showed a thickened dermis with thickened collagen bundles separated by clear
100 spaces with Alcian blue-staining mucin deposition (Figure 2,3). With this findings the

101 diagnoses of scleredema, acne keloidalis and type II diabetes mellitus were made at the same
102 time.

103 Case 2: A 56-year-old woman presented to the our dermatology outpatient clinic for
104 evaluation of possible scleredema. He had a 2-year history of tightness, thickening, and
105 hardening of the skin on her back which had slowly worsened with time. She has diabetes
106 mellitus type II for 15 years and she has been using insulin. She also had chronic renal failure
107 due to uncontrolled hypertension, and on hemodialysis three times a week for 5 years (Figure
108 4).

109 Case 3: A 57-year-old woman presented to the our clinic complaining tightness at her back.
110 She had a 3-year history of thickening of her back which had slowly spreading to neck and
111 arms. She has diabetes mellitus type II for eleven years but she was using her insulin as
112 irregular.

113 Case 4: A 52-year-old woman had a 3 year history of progressive tightness and thickening of
114 the skin in the neck and shoulder region. She had treated with PUVA therapy for 1,5 years in
115 a different dermatology clinic with the diagnosis of morphea 2 years before. She had had
116 diabetes mellitus type II for 10 years.

117 Case 5: A 74-year-old woman was referred from endocrinology clinic for her tightness on her
118 neck and back since she was 64. She has diabetes mellitus type II for 25 years and she has
119 been using insulin and oral antidiabetics.

120 Based on the findings of clinical and histological examination of all cases, a diagnosis of
121 scleredema diabeticorum were made. The characteristics of patients were demonstrated in
122 Table I. Screening for monoclonal gammopathy was unremarkable in all cases. None of the
123 patients has eosinophilia or Raynaud's phenomenon. Antinuclear, antidouble-stranded DNA
124 antibodies, rheumatoid factor, and Scl-70 were not demonstrable. The serology for *Borrelia*
125 *burgdorferi* showed no evidence of infection. No preceding acute infections were found.

126 All patients were started on MTX 15 mg subcutaneously once weekly followed by an
127 1mg/day folic acid other six days. On the three months of the therapy, there were a moderate
128 reduction in the degree of skin thickness, a softening of the skin and a marked improvement in
129 all cases' range of motions. Control biopsies obtained from all of the patients after three
130 months of therapy were compared to their pretreatment biopsies. There were substantial
131 edematous regression and moderate decrease of collagen bundles after the treatment. There
132 were no obvious adverse effects of MTX. A control biopsy of the case 1 was shown in Figure
133 5.

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135 **Discussion**

136 The exact pathophysiology of scleredema and the scleroderma-like syndrome has not been
137 fully elucidated. The accumulation of the extra cellular matrix components seems to be
138 represented by an abnormal expression of extracellular protein genes in skin rather than a
139 decrease of clearing processes.^[8] This gene dysregulation is observed in scleredema
140 regardless of the presence of diabetes. A nonenzymatic glycosylation process due to
141 peripheral hyperglycemia might represent the underlying pathogenic even of aberrant
142 collagen formation. Diabetes is observed in half of the cases of scleredema.^[9,10] Scleredema
143 has been observed in patients suffering from either type 1 or type 2 diabetes mellitus, even if
144 type 2 diabetes seems to be largely more frequent. Duration of diabetes and poor metabolic
145 control were risk factors for the scleredema diabetorum. Indeed, our first case was unaware
146 of his diabetes and we did not have any information about duration of his diabetes.
147 Scleredema may be associated with systemic diseases such as multiple myeloma,
148 hyperparathyroidism, malignant insulinoma, Gougerot-Sjögren syndrome or rheumatoid
149 arthritis in the rare large series published in the literature.^[11,12] Although we examined all our

150 five cases in the laboratory assays, we did not observe any finding related with
151 paraproteinemias or other above-mentioned systemic diseases.

152 The diagnosis of scleredema is based on clinical presentation. Histological confirmation
153 usually not required. On skin biopsy, the epidermis is usually not involved. The dermis tends
154 to be thickened and may be up to four times thicker than a normal dermis. The collagen fibers
155 appear swollen and are separated by wide spaces. The subcutaneous tissue is also involved
156 with fat being replaced by coarse collagen fibers. Mucin deposit is more likely to be observed
157 in the deep dermis and can be stained with Alcian Blue dye.^[1,13] In biopsy specimens, we
158 observed enlarged and thickened collagen bundles within the reticular dermis and increased
159 connective tissue mucin deposits. When the pretherapeutic and posttherapeutic biopsy
160 specimens were examined, we observed that there was substantial edematous regression and
161 moderate decrease of collagen bundles after the treatment.

162 Some eosinophilic syndromes can also cause skin sclerosis. Diffuse fasciitis with eosinophilia
163 (also called eosinophilic fasciitis or Shulman's syndrome) is a rare condition that mimics
164 scleredema with swelling, stiffness, and decreased flexibility of the limbs associated with skin
165 thickening. In addition, there is no occurrence of Raynaud's or GI involvement. Eosinophilia-
166 myalgia syndrome and toxic oil syndrome are toxin-induced disorders that also mimic
167 scleredema. Both conditions result in skin fibrosis and can become chronic.
168 Hypereosinophilia is frequently seen in all these conditions.

169 Although various specific treatments are proposed in the literature, treatment modalities are
170 not completely curative. Numerous therapies have been tried including pituitary extract,
171 thyroid hormones, immunosuppressants, antibiotics, corticosteroids, and physiotherapy;
172 however, none has proven consistently effective.^[4,5,7] MTX, an important immunosuppressant,
173 has been used in patients with scleredema. Although the mechanism of action of MTX in

174 scleredema is unknown, it may suppress or down-regulate the production of fibroblasts or
175 other cells involved with connective tissue or mucin production. Additionally, MTX may
176 interfere with the above-mentioned glycation process.^[7] In 2005 Breuckmann et al revealed a
177 treatment failure in 7 cases diagnosed scleredema diabeticorum treated with an oral dose of 25
178 mg MTX weekly.^[6] Van den hoogen et al. compared MTX with placebo in the treatment of
179 systemic sclerosis and they found that all patients who received MTX for at least 24 weeks
180 responded favourably to MTX therapy with reductions in skin thickness.^[14] However, Seyger
181 et al described a case with severe scleredema diabeticorum partially treated with low dose
182 MTX regimen.^[7] As confirm to this report, in all patients, palpation and inspection showed
183 substantial softening of former affected skin lesions as well as moderate histopathologic
184 improvement resulting in a partially response upon systemic low-dose MTX treatment.
185 In conclusion, the clinical and histological findings obtained from all of our patients
186 demonstrate that MTX therapy may help to treat this rare disease. Further, larger cohort, long-
187 term follow-up studies should be performed to define the role of low-dose MTX in
188 scleredema diabeticorum.

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191 **Conflict of Interest:** No conflict of interest declared by the authors.

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235 Table I. Characteristics of patients

Patient	Age	Sex	Duration of Diabetes	Site of involvement
1	40	Male	New diagnosis	Posterior back, upper neck
2	56	Female	15 years	Back
3	57	Female	11 years	Back
4	52	Female	10 years	Back and neck
5	74	Female	25 years	Back and neck

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Figure legends

Figure 1: The severe thickening of the skin of the neck and back in Case 1.

Figure 2: Biopsy specimens from the upper back of the Case 1 demonstrate the edematous changes seen with scleredema. In the dermis, there are abundant thickened collagen bundles separated by clear spaces. The collagen fibers are also irregularly arranged (H&E, original magnification x100).

Figure 3: Deposits of mucin within the dermis (original magnification x200, Alcian blue).

Figure 4: The severe thickening of the skin of the neck, back and upper arms in Case 2.

Figure 5: A posttreatment control biopsy of Case 1. There are substantial edematous regression and moderate decrease of collagen bundles (H&E original magnification x100)

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