Scleredema Diabeticorum Partially Treated with Low-Dose Methotrexate: a Report of Five Cases

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ABSTRACT

Scleredema is a rare connective tissue disorder that belongs to a group of scleroderma-like disorders. Although no known curative therapy exists, various specific treatments have been proposed in the literature. In this report, we describe five cases of scleredema partially treated with low-dose methotrexate therapy. All patients have diabetes mellitus type II. All patients were started on methotrexate 15 mg subcutaneously once weekly for 3 months. Biopsy specimens were taken from all patients and were examined histologically before the treatment and after 3 months of treatment. All cases partially responded to low-dose methotrexate therapy. We believe that methotrexate therapy may be an alternative therapeutic option in scleredema in view of its efficacy.

Key word: Scleredema, low-dose methotrexate, diabetes mellitus

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Cases

Case 1
A 40-year-old man presented with acneiform lesions on the back of his neck. His medical history was unremarkable. On his dermatological examination, in addition to some acneiform papules on his neck, diffuse hardening of the skin of the back of his neck and upper back were noticed (Figure 1). There was no involvement of the hands or lower extremities. The patient was unaware of this abnormality. His laboratory evaluation revealed a blood glucose level of 303 mg/dL and hemoglobin A1C level of 8.0%. A biopsy specimen from the skin of his back showed a thickened dermis with thickened collagen bundles separated by clear spaces with Alcian blue-staining mucin deposition (Figure 2, 3). With these findings the diagnoses of scleredema, acne keloidalis and type II diabetes mellitus were made at the same time.

Case 2
A 56-year-old woman presented to our dermatology outpatient clinic for evaluation of possible scleredema. She had a 2-year history of tightness, thickening, and hardening of the skin on her back which had slowly worsened with time. She had had diabetes mellitus type II for 15 years and she had been using insulin. She also had chronic renal failure due to uncontrolled hypertension, and had been on hemodialysis three times a week for 5 years (Figure 4).
Case 3
A 57-year-old woman presented to our clinic complaining of tightness in her back. She had a 3-year history of thickening of her back which had slowly spreading to her neck and arms. She had had diabetes mellitus type II for eleven years but was using her insulin as irregular.

Case 4
A 52-year-old woman had a 3 year history of progressive tightness and thickening of the skin in the neck and shoulder region. She had been treated with PUVA therapy for 1.5 years in a different dermatology clinic with the diagnosis of morphea 2 years previously. She had had diabetes mellitus type II for 10 years.

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

Based on the findings of clinical and histological examination of all the cases, a diagnosis of scleredema diabeticorum was made. The characteristics of patients were demonstrated...
in Table 1. Screening for monoclonal gammapathy was unre-
markable in all cases. None of the patients had eosinophilia
or Raynaud’s phenomenon. Antinuclear, antidouble-stranded
DNA antibodies, rheumatoid factor, and Scl-70 were not de-
monstrable. The serology for Borrelia burgdorferi showed no
evidence of infection. No preceding acute infections were
found.

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

Discussion

The exact pathophysiology of scleredema and the sclero-
derma-like syndrome has not been fully elucidated. The accu-
mulation of the extra cellular matrix components seems to be
represented by an abnormal expression of extracellular pro-
tein genes in the skin rather than a decrease of clearing pro-
cesses (8). This gene dysregulation is observed in scleredema
regardless of the presence of diabetes. A nonenzymatic glyco-
sylation process due to peripheral hyperglycemia might rep-
resent the underlying pathogenicity even of aberrant collagen
formation. Diabetes is observed in half the cases of sclerede-
ma (9, 10). Scleredema has been observed in patients suffer-
ing from either type 1 or type 2 diabetes mellitus, even if type
2 diabetes seems to be largely more frequent. Duration of
diabetes and poor metabolic control were risk factors for the
scleredema diabeticorum. Indeed, our first case was unaware
of his diabetes and we did not have any information about the
duration of his diabetes. Scleredema may be associated with
systemic diseases such as multiple myeloma, hyperparathy-
roidism, malignant insulinoma, Gougerot-Sjögren syndrome
or rheumatoid arthritis in the rare large series published in the
literature (11, 12). Although we examined all our five cases
in the laboratory assays, we did not observe any finding re-
lated with paraproteinemias or the other above-mentioned
systemic diseases.

The diagnosis of scleredema is based on clinical presenta-
tion. Histological confirmation is usually not required. On skin
biopsy, the epidermis is generally not involved. The dermis
tends to be thickened and may be up to four times thicker
than a normal dermis The collagen fibers appear swollen and
are separated by wide spaces. The subcutaneous tissue is also
involved, with fat being replaced by coarse collagen fibers.
Mucin deposit is more likely to be observed in the deep der-
mis and can be stained with Alcian Blue dye (1, 13). In biopsy
specimens, we observed enlarged and thickened collagen
bundles within the reticular dermis and increased connective
tissue mucin deposits. When the pretherapeutic and postther-
apeutic biopsy specimens were examined, we observed that
there was substantial edematous regression and a moderate
decrease of collagen bundles after the treatment.

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

Although various specific treatments are proposed in the
literature, treatment modalities are not completely curative.
Numerous therapies have been tried, including pituitary ex-
tact, thyroid hormones, immunosuppressants, antibiotics,
corticosteroids, and physiotherapy; however, none has prov-

Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of diabetes</th>
<th>Site of involvement</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>Male</td>
<td>New diagnosis</td>
<td>Posterior back, upper neck</td>
</tr>
<tr>
<td>2</td>
<td>56</td>
<td>Female</td>
<td>15 years</td>
<td>Back</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>Female</td>
<td>11 years</td>
<td>Back</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>Female</td>
<td>10 years</td>
<td>Back and neck</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>Female</td>
<td>25 years</td>
<td>Back and neck</td>
</tr>
</tbody>
</table>
en consistently effective (4, 5, 7). MTX, an important immunosuppressant, has been used in patients with scleredema. Although the mechanism of action of MTX in scleredema is unknown, it may suppress or down-regulate the production of fibroblasts or other cells involved with connective tissue or mucin production. Additionally, MTX may interfere with the above-mentioned glycation process (7). In 2005, Breuckmann et al. reported treatment failure in 7 cases diagnosed scleredema diabeticorum treated with an oral dose of 25 mg MTX weekly (6). Van den Hoogen et al. (14) compared MTX with placebo in the treatment of systemic sclerosis and they found that all patients who received MTX for at least 24 weeks responded favourably to MTX therapy with reductions in skin thickness. However, Seyger et al. (7) described a case with severe scleredema diabeticorum partially treated with low dose MTX regimen. As confirmed in this report, in all patients, palpation and inspection showed substantial softening of former affected skin lesions as well as moderate histopathologic improvement, resulting in a partially response upon systemic low-dose MTX treatment.

In conclusion, the clinical and histological findings obtained from all of our patients demonstrate that MTX therapy may help to treat this rare disease. Further, larger cohort, long-term follow-up studies should be performed to define the role of low-dose MTX in scleredema diabeticorum.

Conflict of Interest
No conflict of interest was declared by the authors.

References
7. Seyger MM, van den Hoogen FH, de Mare S, van Haelst U, de Jong EM. A patient with a severe scleredema diabeticorum, partially responding to low-dose methotrexate. Dermatology 1999;198:177-9. [CrossRef]