Scleromyxoedema is a rare disease of unknown aetiology that is characterized by progressive cutaneous mucinosis and paraproteinaemia. A variety of systemic (e.g. gastrointestinal, neurological, pulmonary, cardiac and renal) complications may lead to significant morbidity and mortality necessitating therapeutic intervention. The latter remains challenging. Numerous treatment modalities have been reported in the literature, often, however, with inconsistent responses, frequent relapses and potentially serious side-effects. Moreover, the rarity of scleromyxoedema has prevented the execution of controlled therapeutic trials. This paper discusses current proposed therapeutic strategies and reports the case of a 64-year-old male patient with progressive scleromyxoedema associated with IgG-λ paraproteinaemia in whom monthly administrations of vincristine, idarubicin and dexamethasone in addition to daily oral thalidomide led to clinical and laboratory remission within 12 weeks. Key words: chemotherapy, paraproteinaemia, mucinosis.

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Arndt-Gottron scleromyxoedema is a rare fibromucinous disorder regarded as the most generalized variant of lichen myxoedematosus. In contrast to the latter condition, which is usually limited to a restricted area of the skin, has a good prognosis, and does not need any treatment, scleromyxoedema has a chronic, progressive, disabling course and is often associated with systemic, even fatal gastrointestinal (e.g. oesophageal dysmotility), neurological (peripheral neuropathy, encephalopathy), muscular (proximal myopathy, joint contractures), pulmonary (obstructive or restrictive lung disease), cardiac (myocardial infarction), renal (renal insufficiency) or ophthalmological (corneal deposits) manifestations that necessitate immediate and aggressive therapeutic intervention (1–3).

The diagnostic criteria of scleromyxoedema are a generalized papular and sclerodermiform eruption, a monoclonal gammopathy (mostly Ig-λ paraproteinaemia), the absence of a thyroid disorder and a microscopic triad of diffuse mucin deposition within the upper and mid reticular dermis, proliferation of irregularly arranged, large stellate fibroblasts, and fibrosis (2).

Representing the pathological substrate of scleromyxoedema, fibroblasts from affected patients have been found to synthesize a greater quantity of hyaluronic acid than normal fibroblasts and, consequently, a greater amount of mucin accumulates in different tissues (4, 5). Moreover, fibroblasts in scleromyxoedema have been shown to down-regulate proteins involved in growth suppression (MnSOD, Cu/Zn SOD1) and to up-regulate those associated with increased proliferation (stathmin, profiling I, macrophage inhibitory factor), indicating an intrinsic dysregulation of growth homeostasis (4).

In approximately 80% of patients, the disease is associated with a gammopathy (usually IgG-λ, rarely IgG-κ, biclonal IgG/IgA or polyclonal hypergammaglobulinaemia), which possibly reflects a B-cell response to "antigenic" mucin deposition (1, 2, 6, 7). However, although mild plasmacytosis may be found in the bone marrow, scleromyxoedema monoclonal gammopathy is reported to progress to multiple myeloma in only 10% of patients (2).

Although the conspicuous association with paraproteinaemia led to the speculation that the paraprotein itself may act as an auto-antibody, stimulating fibroblasts and mucin deposition (3), measurable paraprotein levels have been shown in various studies to correlate with neither extent, progression or recovery of the disease nor proliferative fibroblast activity (2, 4, 6, 8).

In so far as the distinctive aetiology of the disease thus remains unknown, a specific therapeutic regime has not been established. Moreover, the rarity of scleromyxoedema precludes the definitive evaluation of various treatment modalities that have been reported in the literature with often inconsistent results.

This paper discusses the current proposed therapeutic strategies and reports a case of a patient with progressive scleromyxoedema who responded promptly and dramatically to a new alternative chemotherapeutic regime with vincristine, oral idarubicin and dexamethasone combined with thalidomide.
CASE REPORT

A 64-year-old male patient presented with a 12-month history of erythematous skin induration and areas of lichenoid and sclerodermiform eruptions. Initially limited to the upper arms, the skin lesions were previously diagnosed as myxoedema due to the patient’s autoimmune thyroiditis. However, despite being euthyroid under substitutive therapy with levothyroxine (75 µg/day, 6 days/week; no co-medication) for several years, his skin changes had rapidly worsened within the last 6 months. The papular eruption progressed and coalesced to indurated plaques symmetrically involving most of the integument (Fig. 1A–C). Deep longitudinal facial furrows and intense erythema of the glabella produced a leonine appearance. His skin appeared sclerotic and thickened with limitation in mobility due to joint contractures and sclerodactyly. Furthermore, he complained about hair loss and intermittent fatigue. Histopathology of a biopsy of lesional skin revealed a marked proliferation of irregularly arranged fibroblasts, increased whorled collagen and fibrosis, a sparse superficial lympho-plasmacytic infiltrate as well as a massive deposition of mucin in the upper and mid dermis (Fig. 2). At this site, immunohistochemistry further showed pronounced deposits of \( \lambda \) light chain material.

Full blood count and blood morphology were normal. In serum, levels of creatinine (1.3 mg/dl (0.6–1.2)), albumin (51.1% (54.0–66.0)), gamma-globulins (27.1% (11.0–20.0)), free \( \lambda \)-light chains (46.0 mg/l (5.7–26.3)) and free light chain ratio 0.20 (0.26–1.65) indicated a monoclonal gammopathy IgG/\( \lambda \). The diagnosis of paraproteinaemia was supported by urinary analyses and immunofixation (kappa/lambda ratio in urine 0.28 (1.47–2.95), Bence-Jones proteins negative).

A bone marrow biopsy revealed a mildly hyperplastic haematopoiesis with slightly dysplastic erythro- and megakaryopoiesis as well as an increase in \( \lambda \)-light chain restricted clonal plasma cells (8–10%), consistent with a myelodysplastic syndrome (refractive cytopenia with multi-linear dysplasia (RCMD)) associated with a monoclonal gammopathy of unknown significance (MGUS), type lambda. Putative genetic co-factors (e.g. common single nucleotide polymorphisms) for the concurrence of these two clonal diseases were not found, thus suggesting in our patient to reflect the effect of previous therapies or medications.

Immunohistochemically determined monoclonality in bone marrow demonstrating restriction of \( \lambda \)-light chains was confirmed by fluorescence-activated cell sorting (FACS) analysis of peripheral blood cells. Despite the authors’ awareness of grey zones of clas-

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**Fig. 1.** (A) Scleroderma-like skin induration on the back and typically deep longitudinal (B) glabellar and (C) flexural (knees) furrowing. (D–F) After administration of four cycles of vincristine, oral idarubicin and dexamethasone (VID)-thalidomide, the patient is in almost complete clinical remission. Photographs published with permission from the patient.
sification, multiple myeloma (stage 1) was excluded by (i) repeated quantification of clonal plasma cells in bone marrow, revealing levels that never exceeded 10%, and (ii) subsequent staging including bone scintigraphy and osseo-radiographs that showed no osteolytic foci. A further check-up to assess systemic involvement comprised pulmonary and cardiac evaluations and revealed no relevant pathologies. However, the patient had presumably disease-related neurological symptoms, including a peripheral neuropathy and carpal tunnel syndrome on his right hand.

Based on clinical presentation, histopathology and laboratory data, the diagnosis of scleromyxoedema associated with monoclonal gammopathy IgG/λ of unknown significance was made. The patient underwent an induction regime with intravenous vincristine, oral idarubicin and dexamethasone (i.e. VID schema). Two mg of vincristine were given as a bolus injection on day 1, oral idarubicin at a dosage of 10 mg/m²/day on day 1 to 4 and 20 mg dexamethasone per os daily on days 1–4, 9–12, and 17–20. Treatment cycles were repeated every 28 days, starting on day 29. Concomitantly, our patient received 50 mg thalidomide daily.

After only 2 courses of VID and 4 weeks of oral thalidomide, the clinical picture improved significantly. After administration of 4 cycles (and 12 weeks of thalidomide), the patient was in almost complete clinical remission (Fig. 1D–F). This was accompanied by the normalization of the M-component (gamma-globulins 11.0% (11.0–20.0), free λ-light chains in serum 8.6 mg/l (5.7–26.3), Table I). Without any further treatment, clinical and laboratory remission has persisted for currently more than 6 months of follow-up.

The therapy was well tolerated and repeated evaluations of haematological toxicity remained inconspicuous. Cardiac function in our patient, who had no history of heart disease nor any relevant cardiovascular risk factors, was monitored by sonography pre-, peri- and post-interventionally without any signs of chemotherapeutically induced cardiac side-effects. The only adverse reaction observed was worsening of the pre-existing peripheral neuropathy (which had originally been considered to be a symptom of scleromyxoedema) necessitating withdrawal of thalidomide after 12 weeks of therapy.

**DISCUSSION**

The chronic and potentially fatal course of scleromyxoedema requires an aggressive, yet tolerable therapy, considering that long-term maintenance treatment

<table>
<thead>
<tr>
<th>IgG (mg/dl)</th>
<th>LC-λ (mg/dl)</th>
<th>FLC-λ (mg/dl)</th>
<th>Complete cycles of VID (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2330</td>
<td>474</td>
<td>46.0</td>
<td>Baseline</td>
</tr>
<tr>
<td>1260</td>
<td>234</td>
<td>17.8</td>
<td>1 (4 weeks)</td>
</tr>
<tr>
<td>969</td>
<td>177</td>
<td>15.1</td>
<td>2 (8 weeks)</td>
</tr>
<tr>
<td>760</td>
<td>127</td>
<td>12.7</td>
<td>3 (12 weeks)</td>
</tr>
<tr>
<td>533</td>
<td>86</td>
<td>8.6</td>
<td>4 (16 weeks)</td>
</tr>
</tbody>
</table>

LC: light chains in serum; FLC: free light chains in serum.
is mandatory in most cases. However, evidence of a therapeutic efficacy is quantitatively and qualitatively limited, thereby reflecting the disease rarity and mostly anecdotal, retrospective, uncontrolled and thus highly selective data (Table II) (9). Although the use of cytoreductive melphalan was considered to be a first-line strategy (10), it has been implicated in 30% of deaths secondary to its induction of septic complications and haematological malignancies during long-term therapy (9, 11, 12). Other chemotherapeutic agents for the treatment of scleromyxoedema, such as cyclosporine or cyclophosphamide, have also been used, but with no better results and similar toxic side-effects (11). Alternative approaches, such as systemic retinoids inhibiting fibroblast growth or plasmapheresis to remove pathogenic serum factors showed inconsistent results (9, 11, 12). Intravenous immunoglobulins proved immunomodulatory effectiveness and safety in several studies (1, 7, 9), but high doses and maintenance infusions are commonly required to induce and maintain a clinical benefit, thus making this regime very expensive, with frequently a problem by short supply and time-consuming administration (7). Autologous stem cell transplantation was reported to induce a durable remission in several studies (Table I). However, this approach is not curative and harbours considerable peri-interventional risks, especially if the patient’s general condition is severely compromised by the disease. Recently, the administration of immunomodulatory interferon alpha was associated with worsening in a patient with localized lichen myxoedematous during therapy for chronic active hepatitis C (13) and development of coma one day after the third injection in another (14).

Reconsidering these therapeutic shortcomings and inconsistencies, the pathogenic parallels with multiple myeloma, as well as the widespread and progressive disease in our patient, we introduced an alternative chemotherapeutic regime comprising vincristine, oral idarubicin and dexamethasone (VID schema) combined with thalidomide. The VID schema has been established as an effective and tolerable oral treatment alternative for patients with multiple myeloma to induce cytoreduction (11, 15–17), an effect that is supposed to be beneficial also in scleromyxoedema by interference with plasma cell dyscrasia, fibroblast proliferation and glycosaminoglycan synthesis. In a prospective phase II study evaluating 74 patients with multiple myeloma who had been treated with VID, a partial response was achieved in 57% with previously untreated disease and in 35% with refractory diseases (15). VID thereby does not seem to compromise anti-neoplastic efficacy whilst maintaining the potential to proceed to high-dose chemotherapy or other consolidation strategies. Moreover, it is a tolerable oral alternative in an outpatient setting. Dose escalation up to 13mg/m²/day idarubicin as well as dose reduction to 8mg/m²/day are possible, depending on the patient’s response and toxicity profile. In multiple myeloma, a total of 6–8 courses to induce an anti-tumour effect are commonly applied and well tolerated. Long-term use, however, is contradicted due to the risk of cumulative neuro- and cardiotoxicity.

The rationale for using thalidomide as maintenance therapy in patients with scleromyxoedema was its recognized role in the treatment of refractory multiple myeloma, in which marked and durable responses counteracting plasma cell dyscrasia were obtained with reduction of paraprotein levels (18–22). Moreover, thalidomide has been proposed to be an anti-fibrotic agent through its immunoregulatory effect on pro-inflammatory and pro-fibrotic cytokines in myelodysplastic syndrome with bone-marrow fibrosis and the decrease in gammaglobulin levels in patients with systemic lupus erythematosus (19).

Several case studies of scleromyxoedema indicate a benefit from single long-term thalidomide at a dosage of 150–400 mg/day (18–22) if patients undergo strictly controlled contraception as well as baseline and biannual nerve studies (23). However, the development of neuropathy as a significant adverse event remains a major limitation to an acceptable risk-to-benefit ratio, as documented also in our patient.

Nevertheless, the therapeutic regime presented herein was accompanied by a significant and prompt clinical improvement. It proved effectiveness, efficacy (tolerability) and applicability in an outpatient setting, also when being compared with previously reported treatment modalities. However, the value of this observation again remains limited as long as controlled clinical trials are missing. Moreover, as long as we have to treat this entity “symptomatically”, long-term therapy is necessary, the latter which in case of VID-thalidomide harbour the considerable risk of cumulative toxicities. Nevertheless, short-term application of this regime may be considered as a new therapeutic alternative in the spectrum of reported treatment modalities for scleromyxoedema that may promptly render the patient in a (possibly sustained) clinical and laboratory remission. The consecutive conditioning may facilitate the application of more invasive approaches, such as stem cell transplantation with increased peri-interventional risk.

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Table II. Examples of treatment modalities reported for scleromyxoedema

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>References</th>
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<tbody>
<tr>
<td>Systemic corticosteroids</td>
<td>24–26</td>
</tr>
<tr>
<td>Chemotherapeutic agents</td>
<td>12, 27, 28</td>
</tr>
<tr>
<td>Retinoids</td>
<td>29, 30</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>20, 21</td>
</tr>
<tr>
<td>Intravenous immunoglobulins</td>
<td>7, 9, 31</td>
</tr>
<tr>
<td>Autologous stem cell transplantation</td>
<td>8, 13, 32</td>
</tr>
<tr>
<td>Interferon-alpha</td>
<td>15, 33</td>
</tr>
</tbody>
</table>

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Finally, we would like to emphasize that although our patient had the history of a thyroid dysfunction, histopathological, immunohistochemical as well as laboratory data were clearly consistent with the diagnosis of scleromyxoedema. Considering the fact that he has been evaluated and accurately treated by substitutive medication with levothyroxine for years, we therefore suggest specifying the diagnostic criteria in terms of absence of a manifest thyroid disorder.

The authors declare no conflict of interest.

REFERENCES


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