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SCLEROEDEMA PRECEDING MONOCLONAL GAMMOPATHY BY 30 YEARS

Ami Schattner

The Faculty of Medicine, Hebrew University and Hadassah Medical School, Jerusalem, Israel

Corresponding author's e-mail: amischatt@gmail.com

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ABSTRACT

Three decades after the diagnosis of scleroedema (Buschke's disease), a benign chronic sclerotic skin condition of unknown pathogenesis without systemic involvement, a patient developed secondary gout and normocytic anaemia. Investigations revealed monoclonal gammopathy of undetermined significance, with 1.3 g/dl immunoglobulin G-lambda in the gamma region, a clinically important albeit rare scleroedema-related manifestation, with associated low complement component 4 levels and Coomb's positivity, but no myeloma or amyloidosis.

KEYWORDS

Scleroedema, monoclonal gammopathy of undetermined significance (MGUS), myeloma, beta-2 microglobulin, complement component 4 (C4)

LEARNING POINTS

- Scleroedema (of Buschke) is an unusual sclerotic skin condition grouped together with localised scleroderma, systemic sclerosis, and scleromyoedema.
- Scleroedema has three important systemic associations: a preceding streptococcal infection, type 2 diabetes, and monoclonal gammopathy of undetermined significance (MGUS).
- Scleroedema can precede the appearance of monoclonal gammopathy by decades, and these patients need to be monitored for the development of plasma cell disorder, from MGUS to multiple myeloma.

INTRODUCTION

Sclerotic skin conditions are characterized by excessive collagen deposition and fibrotic changes in the skin and subcutaneous tissue, as well as different associated systemic involvement. All have in common skin thickening or sclerosis, but differ markedly in their pathogenesis, non-dermatological manifestations, and prognosis. Scleroedema (completely different from scleroderma, another sclerotic condition) is poorly recognized, yet has important associations, that are of interest to clinicians beyond dermatology alone.

CASE DESCRIPTION

A 73-year-old man developed acute gouty arthritis (bilateral metatarsophalangeal joints, ankles), improving with treatment (C-reactive protein from 203.6 mg/l down to 1.0

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mg/l). Allopurinol/colchicine were started (uric acid from 9.7 mg/dl down to 6.2 mg/dl). However, the absence of family/personal history of gout, and new-onset anaemia (haemoglobin 9.1 g/dl, previously 13.7 g/dl) prompted a work-up for an underlying disease, despite a normal physical examination.

The patient had been diagnosed thirty years prior with scleroedema (Buschke's disease), confirmed by skin biopsy. Symmetric hardening of the skin was noted at the posterior aspect of the neck and shoulders, extending down the torso *(Fig. 1)*. The levels of white blood cells/platelets were normal, and anaemia slowly improved (12 g/dl). He had primary hypertension, chronic kidney disease (estimated glomerukar filtration rate 52.3 ml/min, normal sediment), and left ventricular hypertrophy/diastolic dysfunction on echocardiography. Electrolytes, calcium, liver enzymes, and lactate dehydrogenase were normal. Protein electrophoresis and immunotyping demonstrated immunoglobulin (Ig) G-lambda 1.3 g/dl in the gamma region. Free light chains lambda were 124 mg/l (normal range 5.7-26.3 mg/l) with normal kappa and abnormal kappa/lambda ratio 0.1 (0.26-1.65). Urine immunoelectrophoresis showed physiological proteinuria. Beta-2 microglobulins were 4369 µg/l (970-2640 µg/l), Coomb's direct was positive (without hemolysis), and complement component (C) 4 was decreased to 7.9 mg/dl (15-53 mg/dl) with normal C3 levels. Rheumatoid factor, autoantibodies, cryoglobulins and hepatitis B virus/hepatitis C virus were not found. Skeletal computed tomography scan was negative for bone lesions. Cardiac magnetic resonance imaging showed no amyloidosis, and buccal and bone marrow biopsies were negative for amyloid and myeloma (8% plasma cells). Over the next 5 years of follow-up, no new findings developed. The laboratory remains pathological but unchanged with the same 1.3 g/dl monoclonal spike.

DISCUSSION

Scleroedema is a rare sclerotic skin disease characterized by slow onset and slow persistent progression of diffuse symmetric thickening and non-pitting 'woody' induration of the skin, involving primarily the neck and upper trunk, sparing the hands and devoid of any extra-dermatological manifestations[1]. Mean age at diagnosis is 54 years[2]. The histopathology reveals thickened reticular dermis with marked swelling of collagen bundles, separated by excessive dermal mucin deposition. Intact epidermis and absence of fibroblast proliferation are important negative features. The pathogenesis is poorly understood, and no evidence-based treatment is known, although patients' activities might be impaired (e.g. bending). Three major internal medicine associations of scleroedema have been identified, best reported in the only case series published of 44 patients[2]. A preceding streptococcal infection was noted (so called "type I" which typically resolves spontaneously), but the most common association is type 2 diabetes, often poorly controlled (68%). Diabetes seems the predominant internal medicine association of scleroedema, although many cases may not be recognized. An old prospective study of 484 patients with diabetes on the west coast of the United States, identified scleroedema in 2.5%[3]. So called "scleroedema diabeticorum", remains an established dermatological manifestation associated with diabetes, and several interventions may be effective, though firm data is scarce[4]. Plasma-cell neoplasms (9%) are the other major association of scleroedema ("type II"), in particular monoclonal gammopathy of undetermined significance (MGUS), as in this case[2]. Here, scleroedema preceded the appearance of monoclonal IgG-lambda by 30 years, an exceptionally long interval. In the literature, scleroedema was recently classified among 'monoclonal gammopathies of cutaneous significance'[5], and indeed, it



Figure 1. *The patient's neck and upper back showing wide symmetric induration of the skin, easily felt on palpation.*

had also been reported in association with smoldering myeloma or multiple myeloma, as well as Waldenstrom macroglobulinemia[6,7]. In a few reports, patients with scleroedema/MGUS progressed to multiple myeloma[8]. We found only ~20 reported patients (PubMed since inception, search terms: scleroedema AND monoclonal gammopathy OR myeloma). All are described as single case reports. The monoclonal spike is often IgA-kappa in the β-globulin fraction. Our patient's IgG-lambda in the gamma region is distinctly unusual. However, it was described in one of the three patients reported in what, to the best of our knowledge, is the first report of the association[9]. Individual reports vary, and scleroedema may also develop in a patient with established MGUS, and notably, a few of the patients had underlying ankylosing spondylitis[8,10]. Treatment approaches must be based on anecdotal evidence only, due to the rarity of the syndrome, unless myeloma is associated[11]. Recently two reports of intractable scleroedema responsive to treatment have been published. In the first, a striking improvement in debilitating scleroedema was achieved with bortezomib-based regimen (bortezomib, cyclophosphamide, and dexamethasone), that was accompanied by a concurrent decrease in paraprotein levels[12]. In the second report, daratumumab (an anti-CD-38 monoclonal antibody) monotherapy led to rapid improvement after 4-5 cycles, sustained over 20 cycles, with mobility recovery, partial histologic regression, and paraprotein disappearance[13].

Another notable feature in our patient was the isolated complement component 4 (C4) decrease, with no evidence of any complement-mediated pathology. This was previously reported in IgG paraproteinaemias and due to classical pathway complement consumption by paraprotein. An inverse correlation between paraprotein concentration and C4 levels had been demonstrated[14]. In conclusion, scleroedema patients who have no diabetes may have an occult MGUS, or are at risk of developing it; this is an association important to clinicians since MGUS is an established premalignant precursor of a clonal plasma cell disorder, with an estimated risk of malignant progression of 1% per year, and rarely to amyloid light chainamyloidosis[15,16]. Monitoring of such patients is warranted.

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