BRIEF ARTICLES

Adjunct Treatment of Recalcitrant Hand Plaques in Nephrogenic Systemic Fibrosis After Imatinib Therapy

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ABSTRACT

Nephrogenic systemic fibrosis (NSF) is a sclerotic disorder presenting with painful indurated plaques and skin thickening involving the trunk and extremities, which can lead to tethering and joint contractures. NSF most commonly affects patients with renal insufficiency who have been exposed to gadolinium. We present a case of NSF involving the bilateral hands, knees, and lower extremities developing over 10 years after gadolinium exposure. Initial improvement was noted in the lower extremities after initiation of imatinib mesylate therapy, but recalcitrant, thickened hand plaques caused persistent pain and functional limitation. Adjunct intralesional corticosteroid injections produced durable softening of the recalcitrant lesions with considerable functional improvement in hand mobility. Based on our experience, intralesional corticosteroid injections appear to be an effective adjunct treatment in patients with incomplete response to anti-fibrotic therapies.

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) is a systemic fibrosing disorder most commonly identified in patients with impaired renal function. NSF presents with painful, sclerotic cutaneous plaques frequently distributed over the extremities and trunk, although visceral involvement has also been reported.[1] Progressive involvement of peri-articular soft tissues may lead to joint contractures and significant functional limitation.[2]

While the pathogenesis of NSF remains elusive, most cases occur in patients with renal dysfunction, particularly those exposed to gadolinium-based contrast agents (GBCA) used in magnetic resonance imaging (MRI).[2] Gadolinium, poorly excreted in the setting of renal insufficiency, is hypothesized to deposit in tissues and induce fibrosis by stimulation of monocytes, macrophages, and fibroblasts.[3]

Imatinib mesylate (Gleevec; Novartis, Basel, Switzerland), a tyrosine kinase inhibitor, has demonstrated efficacy in the treatment of systemic sclerosing disorders, including

NSF, in small case series,[4-7] with notable softening and regression of fibrosis, likely related to interference with the pro-fibrotic TGF-β and PDGF pathways.[5] However, despite promising results, refractory disease is common.

We present a case of NSF with significant functional limitation refractory to systemic imatinib therapy successfully treated with intralesional corticosteroid injections.

CASE REPORT

A 51-year old male presented with an approximately six-month history of thickened skin plaques beginning over the left palm, with subsequent spread to involve the bilateral palms, fingers, knees, elbows, and lower legs. These lesions were associated with pain and decreased range of motion, predominantly in the hands and knees, with occupational limitation (patient worked as a chef) and difficulty ambulating and riding a bicycle. His past medical history was notable for hemodialysis-dependent end-stage renal disease secondary to vesicoureteral reflux, with previous exposure to gadolinium-based contrast agents (GBCA) >10 years prior to presentation.

Physical exam was remarkable for markedly firm, flesh colored plaques most notably on the thenar eminences and overlying the metacarpophalangeal (MCP) joints of the second, third, and fourth digits with extension to the proximal interphalangeal (PIP) joints. (Figure 1) Flexion contractures of the PIP and distal interphalangeal (DIP) joints as well as limitations in finger extension were noted bilaterally. (Figure 2, 3) The knees were similarly thickened, with indurated, “woody” plaques overlying both knees and pretibial shins. The modified Rodnan skin thickness score (MRSS),[8] a clinical tool commonly used in the evaluation and management of systemic sclerosis, was calculated to be 32.

A skin biopsy of the palm demonstrated a fibrotic dermis, with increased mucin deposition and an increased number of CD34+ dermal fibrocytes suggesting a fibrosing dermopathy. Tissue sent to the Mayo Clinic Laboratory revealed a tissue gadolinium concentration of 3.9 mcg/g (ref. range < 0.5 mcg/g) by mass spectrometry.

The patient was diagnosed with nephrogenic systemic fibrosis and started on 400 mg of daily imatinib, with rapid initial response most evident over the lower extremities and knees, and a reduction in MRSS to 20. Despite initial improvement, persistently thickened palmar nodules continued to cause pain and functional limitation even after five months of imatinib therapy.

Given his persistent acral disease and associated occupational limitation, we elected for adjunct therapy with intralesional triamcinolone acetonide injections. The procedure was initially poorly tolerated due to significant pain and difficulty injecting the solution into thick, fibrotic lesions, but 6 mL and 8 mL of 40 mg/mL intralesional triamcinolone acetonide were successfully injected across the palms and volar fingers by our hand surgeon under medial and ulnar nerve blocks during two separate sessions approximately four weeks apart.

After intralesional corticosteroid injections, our patient noticed rapid improvement in occupational dexterity, with markedly improved finger flexion and extension bilaterally, along with notable reduction in size of his indurated hand lesions. (Figures 2 and 3) The injections were well-tolerated, and no systemic or local corticosteroid adverse effects have been noted. He

continues to have excellent response after nine months of follow-up, and has not required additional intralesional therapy.

Figure 1. Thickened palms and proximal digits before (A, B) and after (C, D) intralesional corticosteroid injection. There is notable thinning of the proximal digits and palms post-injection.

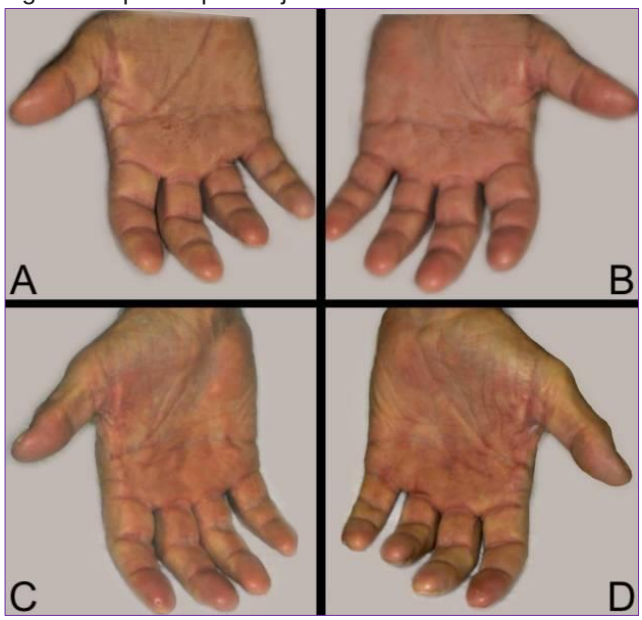


Figure 3. Limitation in finger flexion before (A, B) and after (C, D) intralesional corticosteroid injections. Notable improvement in range of motion of the finger joints post-injection.

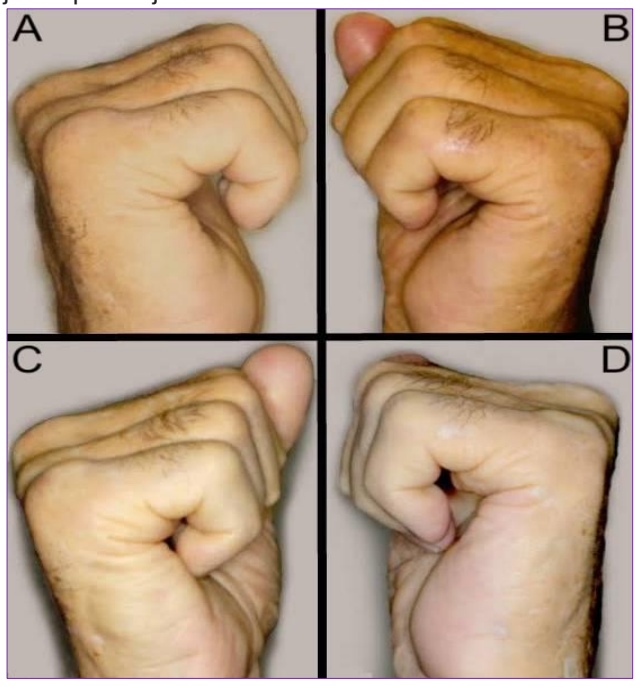
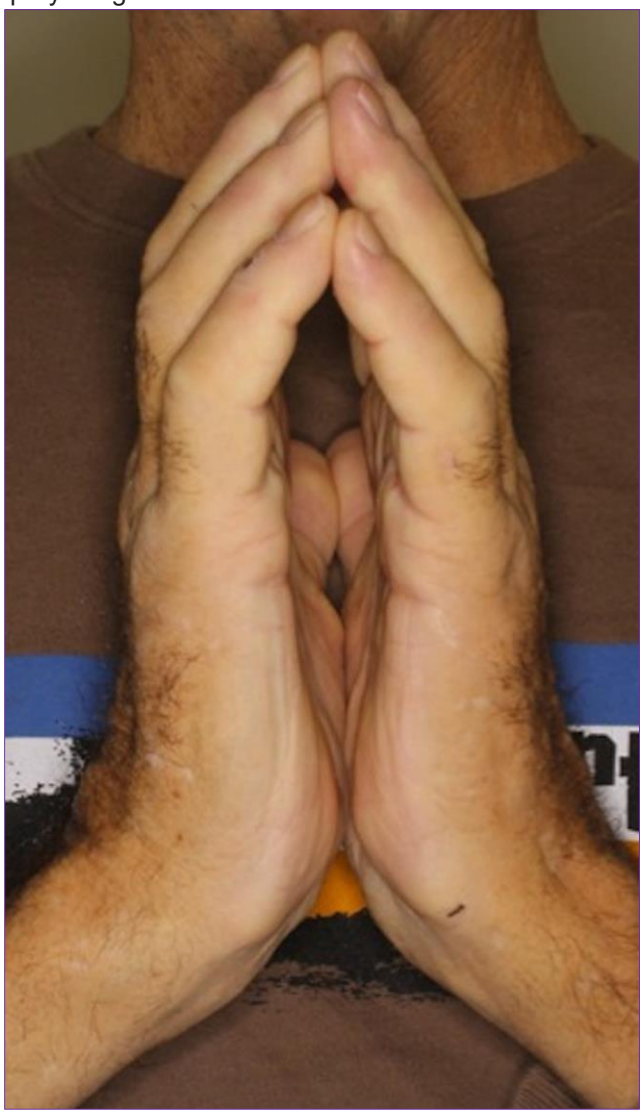


Figure 2. Flexion contractures of the bilateral fingers with thickening of the proximal digits and a positive "prayer sign".



DISCUSSION

Nephrogenic systemic fibrosis (NSF) is a sclerosing disorder most commonly affecting patients with impaired renal function who have been exposed to gadolinium-containing contrast media.[1, 2] While most cases of NSF develop within weeks to months after receiving GBCA, our case presented with a relatively rapid course after over a decade of latency following gadolinium exposure. Taken in conjunction with a recent report of NSF developing >10 years after GBCA,[9] NSF should be a diagnostic consideration in sclerotic disorders in renal dysfunction patients, even with remote GBCA exposure.

Intralesional corticosteroids have been well documented to induce collagen disintegration and reduction in fibroblast density and activity, in addition to their inherent anti-inflammatory properties.[10] While the use of intralesional corticosteroids to treat a sclerosing condition may not be entirely novel, the use of adjunct intralesional corticosteroids has not been previously documented as an effective treatment in cases of NSF refractory to systemic therapies.

Similar to other published reports,[5-7] our patient initially responded well to imatinib therapy, an efficacious treatment in fibrotic disorders.[4-8, 11] It should be noted, however, that while our patient had an initial reduction in MRSS, it did not entirely normalize. This correlates with other published reports of persistent sclerotic disease despite systemic therapy.[6] Since the MRSS is a global assessment of skin fibrosis, it seems that complete resolution, or "normalization," is unlikely given isolated areas of recalcitrance, particularly in patients presenting with widespread or severe fibrosis. With this in mind, the goal for NSF therapy, rather than "chasing" the MRSS number, may instead be to target specific recalcitrant lesions in order to improve functional status. In our case, our patient demonstrated a durable response after nine months of follow-up, with limited local or systemic adverse effects and with dramatic functional improvement after two intralesional corticosteroid injections.

With incomplete response to anti-fibrotic therapies being common, we believe our case highlights the utility of targeted intralesional corticosteroid injections as a useful adjunct strategy in the management of challenging sclerotic conditions.

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