

Nodular Scleroderma in a Patient With Chronic Hepatitis C Virus Infection: A Coexistent or Causal Infection?

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PRACTICE POINTS

- Nodular scleroderma is a rare form of cutaneous scleroderma that can occur in association with systemic scleroderma or localized morphea.
- The clinical features are characterized by solitary or multiple, firm, long-lasting papules or nodules on the neck, upper trunk, and proximal extremities.
- The pathogenesis is still unclear. Some reports have suggested that matricellular protein and growth factor, acid-fast bacteria, organic solvents, or the hepatitis C virus may be involved.

Nodular scleroderma is a rare form of scleroderma that may occur systemically or locally. The pathogenesis of this variant is unknown. We report the case of a 63-year-old woman with systemic scleroderma and chronic hepatitis C virus (HCV) infection who had numerous papules and nodules on the neck and trunk. Skin biopsies from her lesions revealed characteristic findings of scleroderma. This case not only depicts the rare entity of nodular scleroderma but demonstrates the association of HCV infection with systemic autoimmune diseases such as scleroderma.

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Case Report

A 63-year-old woman was referred to our clinic for evaluation of multiple papules and nodules on the

neck and trunk that had been present for 2 years. Three years prior to presentation she had been diagnosed with systemic sclerosis (SSc) after developing progressive diffuse cutaneous sclerosis, Raynaud phenomenon with digital pitted scarring, esophageal dysmotility, myositis, pericardial effusion, and interstitial lung disease. Serologic test results were positive for anti-Scl-70 antibodies. Antinuclear antibody test results were negative for anti-double-stranded DNA, anti-nRNP, anti-Ro/La, anti-Sm, and anti-Jo-1 antibodies. The patient was treated with prednisolone 7.5 mg daily, nifedipine 15 mg daily, valsartan 80 mg daily, manidipine 20 mg daily, omeprazole 20 mg daily, and beraprost 80 µg daily. One year later, numerous asymptomatic flesh-colored papules and nodules developed on the neck, chest, abdomen, and back. There was no history of trauma or surgery at any of the affected sites.

On further investigation, anti-hepatitis C virus (HCV) antibodies were identified and confirmed by HCV ribonucleic acid polymerase chain reaction at the same time that the diagnosis of SSc was established. Hepatitis C virus genotype 3a was noted, and the patient's viral load was 378,000 IU/mL. Therefore, a diagnosis of chronic HCV infection was established. The patient was initially unable to receive medical treatment due to lack of

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The authors report no conflict of interest.

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finances. A year and a half following the diagnosis of HCV infection, with worsening liver function tests and increasing viral load (1,369,113 IU/mL), the patient began therapy with peginterferon alfa-2b 80 µg weekly and ribavirin 800 mg daily. However, the medications were discontinued after 2 months when she developed severe hemolytic anemia related to ribavirin.

On physical examination, the patient was noted to have a masklike facies with a pinched nose and constricted opening of the mouth. Her skin was tightened and stiff extending from the fingers to the proximal extremities. Numerous well-circumscribed, flesh-colored, firm papules and nodules ranging from 2 to 20 mm in diameter were present on the neck (Figure 1), chest, abdomen (Figure 2), and back.

Two 4-mm punch biopsy samples obtained from a papule on the neck and a nodule on the abdomen revealed homogenized collagen bundles with scattered plump fibroblasts in the lower

reticular dermis. Clinicopathologic correlation of the biopsy findings with the cutaneous examination resulted in a diagnosis of nodular scleroderma (Figures 3 and 4).

The patient began treatment with intralesional injections of triamcinolone 5 to 10 mg/mL for nodules as well as an ultrapotent corticosteroid cream, clobetasol propionate 0.05%, for small papules. Injections were performed at 4- to 8-week intervals and resulted in modest clinical improvement.

Comment

Scleroderma may be present only in the skin (morphea) or as a systemic disease (systemic scleroderma). Rarely, cutaneous involvement can exhibit a nodular or hypertrophic morphology, which has been described in the literature as nodular or keloidal scleroderma in a patient with known SSc¹⁻¹⁰ and as nodular or keloidal morphea in localized cutaneous scleroderma.^{3,11-13}



Figure 1. Numerous flesh-colored firm papules and nodules on the posterior aspect of the neck.



Figure 2. Multiple well-defined sclerotic papules and nodules on the abdomen.

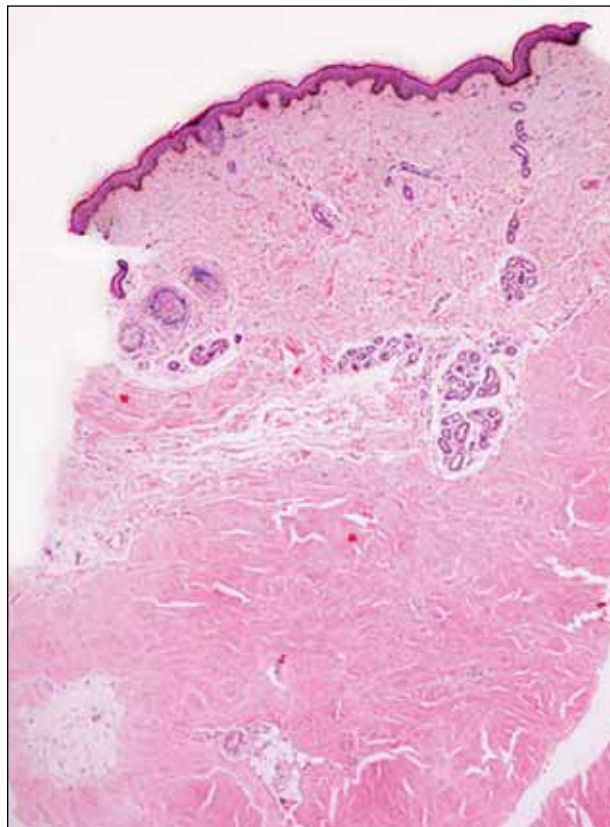


Figure 3. The collagen bundles in the reticular dermis appeared thickened and closely packed. They stained more deeply eosinophilic than in the upper dermis. The overlying epidermis was normal (H&E, original magnification ×4).

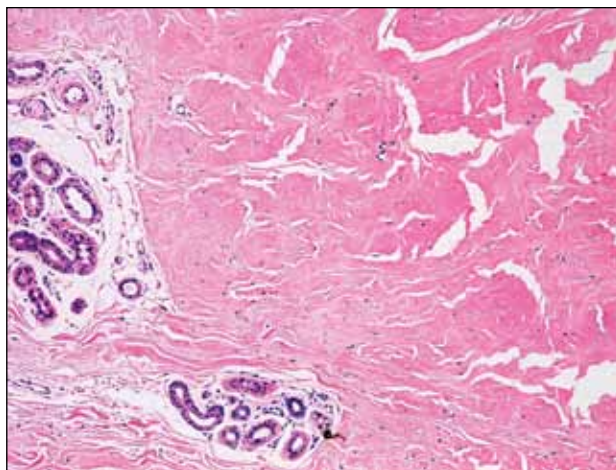


Figure 4. Thick, pale, hyalinized collagen bundles with scattered fibroblasts were seen in the lower reticular dermis. The eccrine glands were surrounded by sclerotic collagen and only a few adipocytes (H&E, original magnification $\times 20$).

Histopathology—The distinction between the terms *nodular scleroderma* and *keloidal scleroderma* is not clear, and they are not necessarily interchangeable. To provide clarity, we find it useful to delineate specific histologic findings associated with the diagnoses of keloid, scleroderma, and the uncommon keloid/scleroderma overlap. The histopathologic findings of keloids include a fibrotic dermis and broad dispersed bundles of eosinophilic hyalinized collagen. The histopathologic findings of scleroderma include broad sclerotic bands of collagen throughout the dermis with loss of perieccrine fat. In the overlapping keloid/scleroderma condition, which is a variant of scleroderma, hyalinized collagen fibers and keloidal collagen appear in the same specimen.^{3,4}

To distinguish these conditions, Barzilai et al⁵ proposed that only cases showing both clinical and histologic characteristics of a keloid should be referred to as keloidal morphea/scleroderma. They further stated that the terms *nodular morphea* or *nodular scleroderma* ought to be used only for cases that are indistinguishable histologically from scleroderma. The term *morphea* is appropriate when only a limited amount of skin disease is present, while *scleroderma* implies association with systemic disease.⁵ Likely, there is a histologic continuum in this variant of scleroderma, in which nodular morphea/scleroderma exists at one end and keloidal morphea/scleroderma exists at the other end.^{5,13}

In the case of our patient, papulonodular lesions developed 1 year after the diagnosis of SSc was made, and the histopathologic examination revealed classic findings of scleroderma. As a result, our

patient is most appropriately classified as having nodular scleroderma.

Clinical Features—Nodular scleroderma mostly affects young and middle-aged women and is clinically characterized by solitary or multiple firm, long-lasting papules or nodules on the upper trunk and chest, neck, and proximal extremities.^{1-4,6}

Etiology and Pathogenesis—The triggers and cellular mechanisms of nodular scleroderma are unclear. Some authors have implicated matricellular protein and growth factors such as tenascin, connective tissue growth factor, and epidermal growth factor in nodule formation.^{7,8,11} Yamamoto et al⁹ cited chemical exposure to a silica-containing abrasive as the cause of nodular scleroderma in a worker.

Possible HCV Association—Some reports have indicated an association between nodular scleroderma and pathogens such as acid-fast bacteria¹⁰ and HCV.⁶ Of note, many extrahepatic conditions have been associated with HCV infection, such as membranoproliferative glomerulonephritis, cutaneous vasculitis, lichen planus, and porphyria cutanea tarda.¹⁴

The association of HCV infection with systemic autoimmune disease (SAD) has been described in a number of instances; cryoglobulinemia has most commonly been linked to HCV.¹⁵ Although the association between HCV and other SADs is less clear, there is growing interest in a possible relationship between them. To that end, physicians of the HISPAMEC (Hispanoamerican Study Group of Autoimmune Manifestations Associated With Hepatitis C Virus) study group described the clinical and immunologic characteristics of 1020 patients with SAD and associated chronic HCV infection. The 3 most frequent SADs (>90% of cases) were Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus.¹⁶ However, the strength of association differs for each SAD based on existing descriptions.^{16,17} Less commonly, there may be a causal relationship between HCV infection and SSc. It should be noted that most of these data are based on small series and case reports.^{6,16-19}

The role of HCV in the pathogenesis of systemic scleroderma and other autoimmune diseases is unknown. It is also possible that the replication of HCV outside the liver, particularly in mononuclear cells, may suppress immune tolerance in genetically predisposed individuals.²⁰

Conclusion

Nodular scleroderma associated with HCV infection is a rare entity. At present, it cannot be determined whether there is an etiopathologic association between HCV infection and SSc or whether the simultaneous diagnosis may be coincidental. Routine

determination of HCV serology in scleroderma patients may help to clarify this issue.

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