Clinical and histological findings in nephrogenic systemic fibrosis

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Abstract

Nephrogenic systemic fibrosis (NSF) is a relative newcomer to the world of medicine. NSF was introduced just over 10 years ago as nephrogenic fibrosing dermopathy, but with further investigation, its systemic nature was determined. The strict adherence to a definition requiring both clinical and pathological concordance has allowed for careful separation of this entity from other fibrosing disorders, leading eventually to the realization that gadolinium-based contrast agents were closely associated with its onset. As planned prospective studies get underway, it is of paramount importance that researchers and clinicians realize that NSF remains a very challenging diagnosis, and that both clinical and histopathological criteria must be employed to reach the most accurate diagnosis possible.
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1. Introduction

Nephrogenic systemic fibrosis (NSF), first characterized in 2000 [1], has been the subject of intense clinical and epidemiological examination in recent years. Because of the strong association between the onset of NSF and the exposure of renally impaired patients to gadolinium-based contrast agents (Gd-CA) [2,3], there has been a major interest in identifying specific clinical and histological findings. This goal has remained elusive, as no feature by itself is absolutely specific for NSF, and even combinations of histological and clinical features of NSF may be seen in other disease entities. The purpose of this review is to consider the breadth of dermatological and dermatopathological features one can encounter in NSF, and offer insight into narrowing the clinicopathological differential.

2. Dermatological findings in NSF

The following characteristics are gleaned from a review of the NSF literature encompassing a total of 130 reported patients, as well as our personal experience at Yale University.

2.1. Chronology

The typical clinical course of NSF begins with swelling of the distal extremities. Edema beyond the patient's baseline is common with NSF (32%). When edema is present, it can resolve, leaving firm plaques that progress to more extreme brawny induration and thickening of the affected skin. Some patients may present with deep NSF skin lesions relatively early and rapidly, and conversely, more superficial lesions may appear on patients long after established, deep involvement has occurred. In some cases, NSF progresses to marked physical disability characterized by almost complete loss of range of motion of all extremity joints. While NSF sometimes stabilizes, it rarely spontaneously remits. Restoration of renal dysfunction (via medical or surgical means) usually results in stabilization or regression of lesions.

2.2. Symptomatology

In the majority of NSF patients, symptomatic skin involvement was the initial indication of disease. NSF patients most often report pain (52%), followed by pruritus (36%), joint stiffness (34%), tightness (30%), swelling (25%) of the hands and feet, paresthesias (24%), and burning (16%) (Table 1). Patients have also reported weakness, palpable warmth, and causalgia [1,4,5]. Several patients have described costochondral pain.

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Table 1
NSF cutaneous symptoms

Pruritus	36%
Burning	16%
Pain	52%
Tightness	30%
Swelling	25%
Paresthesia[a]	24%
Joint stiff	34%

[a] Includes tingling, numbness, and/or prickling sensations.

Table 2
NSF cutaneous lesion distribution

Hands	34%
Upper extremities	66%
Lower extremities	85%
Feet	24%
Buttocks	9%
Trunk	23%
Face	3%

2.3. Lesional distribution, morphology, appearance and texture

In the majority of NSF patients, the earliest lesions appear on the lower extremities, followed by the upper extremities and the trunk. The skin involvement is often symmetrical and bilateral. Skin lesions were said to be localized in decreasing order of frequency to the lower extremity (85%), upper extremity (66%), trunk (35%), hands (34%), feet (24%), buttocks (9%), and face (3%) (Table 2).

The skin may be variably affected with subtle, superficial papules and plaques, deeper dermal or subcutaneous induration, and severe contractures of the joints. The most frequently seen lesions are plaques (58%), papules (32%), and nodules (17%) (Table 3). Additionally, macules [6,7], vesicular lesions, blisters, bullae and ulcers [1,5,8,9] which later progressed to become plaques have been reported in case reports. Many NSF patients may have subtle superficial findings initially. As these become more advanced, patterning may be appreciated. Papules often coalesce into plaques, and the edge of lesions may have a distinctive irregular, finger-like (or "amoeboid") edge with areas of sparing [10] or may be more reticulated.

The skin may also show changes in pigmentation and color. Hyperpigmentation (41%) and erythema (39%) are seen in NSF

Table 3
NSF cutaneous lesion morphology

Papules	32%
Plaques	58%
Nodules	17%
Erythema	39%
Induration	78%
Hyperpigmentation	41%
Contracture	50%
Edema	32%
Blisters/ulcers	2%
Hair loss	2%

Fig. 1. Superficial, rough appearing, pink plaques are an early finding in NSF.

patients. Hypopigmentation has been reported rarely [11]. In our review of the literature, color was not described for every patient, but flesh-colored [8,12], tan [13], yellow [13–15], pink [14], red-orange [16], red [6], grey-brown [17], brown [8,12,18], and violaceous lesions have been observed (Fig. 1). The appearance of the lesions may change with the depth of involvement.

Superficial lesions of NSF can show epidermal changes as revealed by slight overlying scaling to more overt flaking [14,19]. The majority of NSF patients have lesions that are deeper and indurated (78%) (Fig. 2). The indurated plaques have a very firm consistency. The plaques may also be described as thickened, lumpy, furrowed, woody, brawny, 'bound-down' and shiny. When the lesions display sheen, this is a sign of deeper

Fig. 2. Red-brown, indurated plaques indicate deeper skin involvement with NSF.

Fig. 3. In progressive NSF, the skin becomes fibrotic with a shiny appearance and subcutaneous tissue is diminished.

Fig. 4. Contractures seen in the distal upper extremities are common in NSF.

Fig. 5. Contractures seen in the distal lower extremities are common in NSF.

Fig. 6. Prominent yellow scleral plaque in a patient with NSF.

involvement of the dermis (Fig. 3). When there is extensive dermal involvement, the skin may pucker at the hair follicles, giving a "peau d'orange" (peel of the orange) appearance. Deep dermal and subcutaneous involvement may give the appearance of cobblestoning (e.g. hard bumps, typically on the thighs) and banding (focally depressed linear areas of bound-down skin, typically on the arms or legs).

Many patients experience loss of range of motion in the joints, and overt contractures (50%) involving the extremities (Figs. 4 and 5). The fibrosis can lead to loss of dermal appendages [20]. Patients may progress to almost complete loss of subcutaneous tissue, total involvement of the skin with fibrosis, severe contractures of all extremities and complete loss of range of motion. These are clearly major deforming and functionally compromising components of NSF (Table 3).

While not technically dermatological, telangiectatic to yellowed scleral plaques (Fig. 6) are readily identified bilaterally and symmetrically in most NSF patients [13,14,21].

3. Dermatological differential diagnoses for NSF

Several disorders may manifest skin lesions with similar findings to NSF, but elimination of these from the differential

diagnosis is substantially aided by consideration of the history, certain histologic tendencies, and distinguishing lesional morphology and distribution. Differential considerations for NSF include lipodermatosclerosis, scleroderma/deep morphea, scleromyxedema, eosinophilic fasciitis, eosinophilia–myalgia syndrome, and chronic-graft-versus-host disease (cGVHD). The manifestations of NSF in comparison to these other conditions can help elucidate the more subtle distinctions.

3.1. Lipodermatosclerosis (LDS)

LDS is characterized by very painful induration of the distal lower extremities, particularly medially and inferior to the knees. LDS occurs very commonly in patients who have edema, most often due to venous insufficiency and vascular stasis. Involvement above the knee is very rare.

3.2. Scleroderma and morphea

Patients with scleroderma/deep morphea typically have additional signs that help to exclude NSF. Scleroderma can affect

multiple internal organs and may show positive autoantibodies, such as SCL-70 and ANA. These patients may develop pigment changes in many areas. Dyspigmentation may be evident along the trunk and forehead, most commonly manifested as a "salt and pepper" pattern of pigment retention at the follicles. Scleroderma patients are also much more likely to demonstrate sclerodactyly, with tapering and pointing of the fingers. They commonly develop minute foci of vascular compromise in their fingertips, associated with Raynaud's disease. Morphea (localized scleroderma) presents as indurated plaques on the trunk or extremities and is not usually associated with systemic involvement. The clinicopathological variant of morphea known as "morphea profunda" presents with thick, tight skin [22,23], often with bound-down bands.

3.3. Scleromyxedema (SCX)

SCX is a condition characterized by cutaneous mucinosis and fibrosis that develops over the arms, and hands, and less often on the legs and trunk. Additionally, SCX commonly will involve the face, which is almost never encountered in NSF. Widespread papules can coalesce to form plaques, with areas of diffuse induration. SCX can result in internal deposits of mucin, resulting in a variety of systemic complaints, including cardiac dysfunction and neurologic signs [1]. As virtually every case of SCX is associated with an underlying gammopathy, these patients require appropriate testing by serum and urine electrophoresis and potentially a bone marrow biopsy to rule out multiple myeloma [24,25].

3.4. Eosinophilic fasciitis (EF)

EF is an inflammatory fibrosing condition of the fascia involving the tissues around the muscles, and may have systemic involvement. EF can manifest several of the findings seen in NSF including deep induration and peau d'orange changes. Often, EF patients manifest peripheral eosinophilia, so a complete blood count with differential can help make this diagnosis. EF patients also may have an underlying polyclonal hypergammaglobulinemia.

3.5. Eosinophilia–myalgia syndrome (EMS)

EMS is linked to the ingestion of the amino acid L-tryptophan. Skin lesions range from erythema with edema, to papules, to diffuse thickening with a peau d'orange appearance. The lesions often begin on the extremities and may spread to the trunk and face. Since the ban of L-tryptophan containing supplements the number of cases of EMS has dropped precipitously.

3.6. Chronic graft versus host disease (cGVHD)

Patients with cGVHD may have very similar clinical findings to those seen in NSF; however, cGVHD is seen in a completely different clinical setting (e.g. after allogeneic stem cell transplantation).

4. Dermatopathological findings in NSF

NSF is characterized by dermal fibrosis [1]. Invariably, there are far more numerous background spindle cells than one normally encounters in the dermis. These cells (fibrocytes) tend to be tapered by hematoxylin and eosin staining (H&E), with indistinct cytoplasmic borders [13,26]. Nuclei may be blunt ended to tapered, and sometimes have a vesiculated chromatin pattern. The fibrocytes are not multinucleated, do not manifest mitotic figures [27], and do not typically demonstrate nucleoli or nuclear membrane irregularities. On occasion subtle granular material may be noted in the cytoplasm. This will stain positively with a Perls' stain, indicating it may be partially composed of hemosiderin.

In early lesions of NSF, collagen bundles may be quite narrow, with abundant edema fluid and/or mucin separating them. The fibrocytes are distributed between the collagen strands, generally parallel to their predominant direction. Glassy elastic fibers can also be identified, also generally in a parallel directional orientation. The fibrocytes are CD34 positive when stained immunohistochemically [26,28]. The staining pattern is membranous, and often reveals a much more complex dendritic network (Fig. 7) than can be appreciated by H&E staining alone. The dendritic processes interconnect, and tend to orient parallel to elastic fibers and collagen bundles. If collagen is cut in cross section, the CD34 positive dendritic processes seem to encircle the collagen bundles [1].

Fibrocytes are also procollagen I positive by immunohistochemistry. This dual positivity (Fig. 8) (CD34 and procollagen I) is characteristic of so-called "circulating fibrocytes," mesenchymal stem cells of bone marrow origin that have been experimentally proven to participate in wound repair [27]. The dermal fibrocytes of NSF are almost certainly largely composed of circulating fibrocytes that have translocated from the bone marrow to the soft tissues [27,29,30], possibly in response to deposited gadolinium.

In early lesions of NSF, while collagen bundles are thin, procollagen I positivity is noted fairly inconspicuously in the perinuclear cytoplasm of the bland dermal fibrocytes. In more advanced disease, collagen bundles become thicker (still generally maintaining clefts of separation between their neighbors) and the cytoplasm of the fibrocytes becomes plump and intensely procollagen I positive [1].

In general, elastic fibers remain present in NSF, and are easily identifiable by H&E and EVG stains [1,13]. As the collagen bundles thicken, the fibrocytes and elastic fibers are wedged between them [32]. Typically, and contrary to sclerosing conditions like morphea and scleroderma, clefts are maintained between individual bundles. In addition, CD34 positivity and elastic fibers tend to remain intact. Sometimes, sandwiched between the fibrocytes and the collagen bundles, there is a myxoid substance that stains with typical mucin stains (alcian blue and colloidal iron) [4,13,26]. This material may also stain in a diffuse manner with procollagen I (Fig. 9), and may represent admixed ground substance and immature collagen. In some cases of NSF, mucin is virtually absent [7].
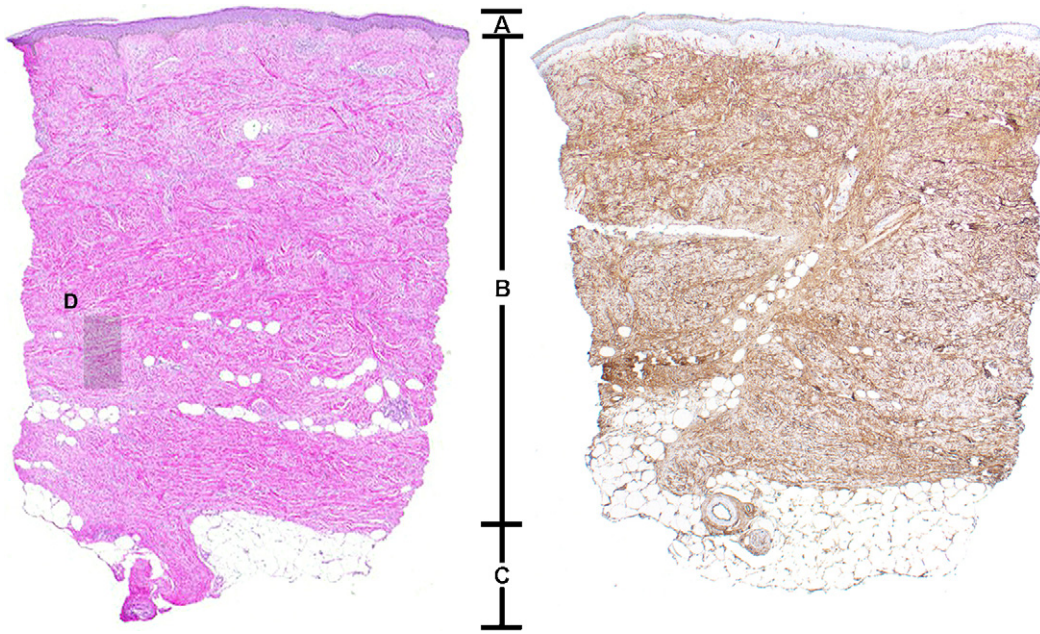
Fig. 7. Low-power image of hematoxylin and eosin stained biopsy on left, with CD34 stained tissue on right. The epidermis is indicated by (A), the dermis by (B), and the subcutis by (C). The D box outlines the equivalent area in Fig. 8. Note the prominent positive staining with CD34 (brown) throughout the dermis, indicating the distribution of fibrocytes in this dermis.
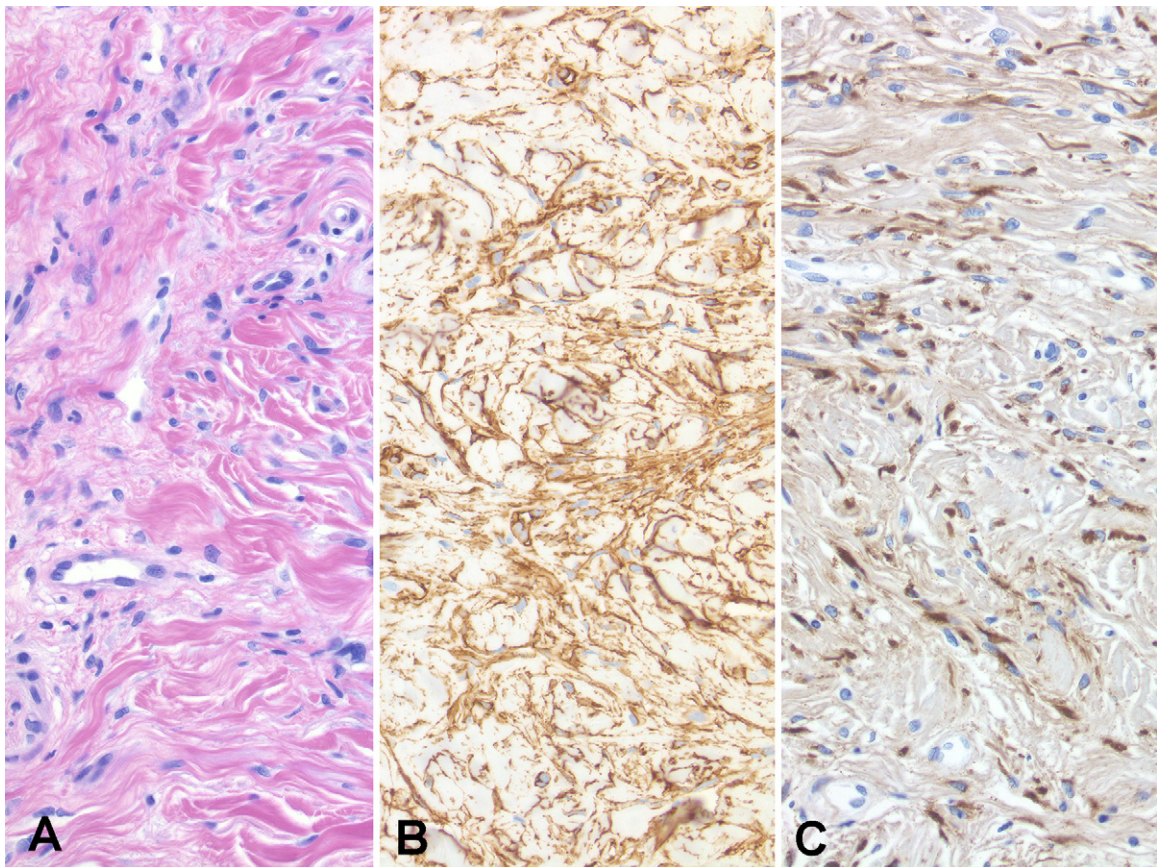

Fig. 8. Magnification of area D in Fig. 7. (A) H&E stain, (B) CD34 stain and (C) procollagen I stain. Many of the elongated cells staining with CD34 also stain with procollagen I. These dual positive cells are fibrocytes.
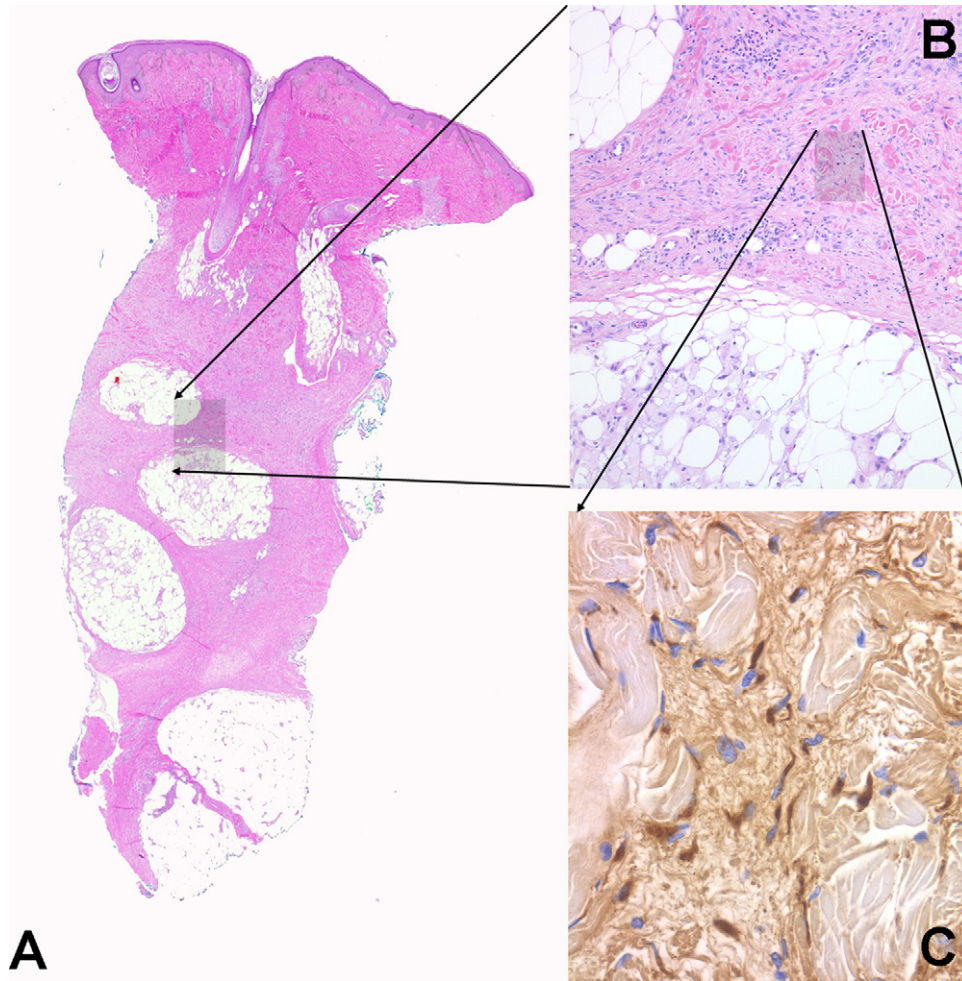
Fig. 9. (A) Scanning image showing markedly thickened subcutaneous septa, (B) magnification showing increased spindle cells, thick, pink collagen bundles, and intervening myxoid material (light pink) and (C) procollagen I stain with dark brown fibrocytes and light brown immature background collagen matrix.

Very uncommonly, spindle cells may diminish in number and focal sclerosis of collagen will be noted (with loss of bundle definition and hyalinization). In these foci, immunohistochemical staining with smooth muscle antigen may be apparent [31,30]. This indicates that some fibrocytes, possibly under the influence of cytokines such as transforming growth factor beta, have assumed a myofibroblastic immunophenotype [31]. This may be an indication of maturation in NSF [30]. Elevated tissue levels of TGF beta mRNA have been identified in NSF [20].

In NSF, the dermis may be fully, or focally, involved by the histopathological pattern noted above [28]. The epidermis is not typically affected by NSF, although longstanding cases may show some degree of basilar pigmentation and epidermal acanthosis. Flattening of the rete pattern is sometimes seen [32]. In some cases, a reduction in the number of dermal appendages has been noted [32]. The subcutaneous septa are commonly markedly widened (Fig. 9) and the fat lobules may be effaced [1,20,31]. In these deeper NSF foci, the widened septa are collagenized in the same manner as described above.

On occasion loose aggregates of epithelioid CD68+ histiocytes are noted in the subcutaneous septa, and multinucleation can be seen (Fig. 10) [1,28]. Some examples of NSF are dominated by large numbers of histiocytes [28], and rarer yet, some contain numerous multinucleated giant cells [33], osteoclast-like giant cells [34], foci of osteoid deposition, and/or calcified bone spicules [28]. Any combination of these features may be seen. Osseous foci forming upon refractile elastic fibers are notable in some cases [28]. Calcification, either within histiocytes, or frankly encrusting thickened collagen and elastic fibers is a common feature [8,13,28,31,33,34]. Calcification within vascular walls is not uncommon [35,36], and does not necessarily imply calciphylaxis.

Overall, vascularity is not typically prominent, although some cases of NSF show evidence of neovascularization, usually manifested as numerous small vascular profiles in the vicinity of fat lobules (typically within septa) [1,28,30,31,34,37]. On rare occasion, we have seen patterns resembling dermal angiomatosis. Despite the association of NSF with hypercoagulability, microthrombi are not present, and vasculitis is not seen. Besides small numbers of bland monocytic cells surrounding blood ves-
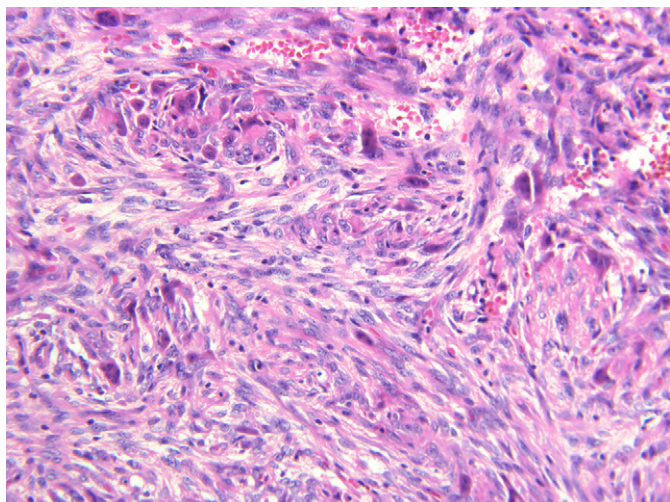
Fig. 10. Plump spindled fibrocytes intermixed with clusters of multinucleated giant cells.

sels, there is characteristically no inflammatory response in NSF [8]. Neutrophils and eosinophils (unless explainable by a superimposed dermatitis) are not seen in NSF [31]. Background mast cells can be conspicuous at times. On rare occasions plasma cells are conspicuous in the infiltrate [28,37]. On one occasion known to the author (SEC) this was associated with concurrent HIV infection.

Besides fibrocytes and histiocytes, increased numbers of factor XIIIa positive dendritic cells may be notable. In some cases, there may be coexpression of factor XIIIa and CD68 in the same cell (the significance of which is unclear) [20,32]. Neither increased numbers of CD68+ histiocytes nor factor XIIIa positive dendritic cells are required to make a diagnosis of NSF [26].

In cases in which large numbers of histiocytes are observed, it is not uncommon to see elastophagocytosis (EP) [28]. In rare cases, EP may be a dominant clinical and histopathological finding, presenting a clinical picture resembling generalized elastolysis [38]. This pattern may be an indication of maturation of the NSF lesion, as it occasionally occurs in the setting of improved renal function. Lastly, a pseudoxanthoma elasticum (PXE) like pattern of elastic fibers has been reported [36], however this specific finding was seen in a patient with concurrent calciphylaxis. Calciphylaxis has been associated with PXE-like elastic fiber changes in a prior publication [39].

Very deep incisional biopsies may show extension of the fibrotic process through the fascia and into the underlying skeletal muscle. In these cases, skeletal muscle fibers may atrophy, surrounded by hyperchromatic, pyknotic nuclei [20,33,40].

Utilization of special techniques (electron microscopy with electron dispersive spectroscopy [EM–EDS] and inductive couple plasma mass spectroscopy [ICP-MS]) has identified the presence of gadolinium within the affected tissues of patients suffering with NSF [41–43]. There is no special staining technique that allows sensitive and specific detection of gadolinium in affected tissues by light microscopy.

5. Dermatopathological differential diagnoses for NSF

5.1. Scleromyxedema (SCX)

Histopathologically, SCX displays numerous stellate and bipolar fibroblasts scattered among thick haphazardly arranged collagen bundles, increased dermal mucin, and infiltrates of lymphocytes and sometimes of plasma cells [1]. Colloidal iron or alcian blue staining at a pH of 2.5 will histochemically demonstrate the mucin, which is typically localized to the reticular dermis. Pools of mucin can accumulate, widely separating the collagen bundles. The immunohistochemical profile of the spindle cells is CD34/procollagen I dual positive, making confident distinction from SCX impossible with this stain pairing.

Some authors have observed that SCX does not typically involve the subcutis, whereas NSF does, making the distribution of the infiltrate within the biopsy a defining characteristic [44]. Unfortunately, frequently the tissue sample is not sufficiently deep to ascertain whether septal involvement is present at all, making this criterion useful only in select situations.

5.2. Scleroderma and morphea

The early changes of morphea and scleroderma are purported to be increased capillary permeability, edema, and dermal mucin. Ultimately, dermal collagen deposition ensues, and in late stages, dermal collagen bundles are thickened, with a loss of retraction artifact (in formalin fixed specimens) between individual bundles. Eventually, periappendageal adipocytes are lost and the collagen ensnares adnexal structures. Elastic fibers may be reduced or inhibited, but this is not a universally reported finding [22,23,45]. Researchers have shown that CD34 positive dendritic cells selectively vanish from the dermis of patients with scleroderma [46]. A sparse superficial and deep perivascular and interstitial lymphohistiocytic infiltrate, sometimes containing plasma cells and eosinophils is characteristic and typically most pronounced in early lesions of scleroderma and morphea [46,47]. A denser infiltrate and involvement of the papillary dermis is seen in morphea, but not scleroderma [45].

NSF can be differentiated from scleroderma and morphea by its pronounced cellularity, virtually absent lymphocytic infiltrate, rarity of plasma cells and eosinophils, persistence of bundled collagen, clefts, and CD34 positive fibrocytes, and near absence of collagen homogenization.

5.3. Eosinophilic fasciitis (Shulman's syndrome)

The histopathological changes seen in EF consist of fascial inflammation, edema, thickening and sclerosis. The thick collagen bundles seen in EF commonly alternate with entrapped fat in parallel layers. The inflammatory infiltrate consists of lymphocytes, plasma cells, histiocytes, and sometimes eosinophils, and may extend into the fibrous septa of the subcutaneous fat. Dermal sclerosis is common [48]. Mucin and factor XIIIa positive dendritic cells are typically bountiful in the fascia. These dendritic cells often extend through the dermis as well [49].

NSF usually has no infiltrate of note (besides perivascular lymphocytes). Both EF and NSF may have widening of the interlobular subcutaneous septa.

5.4. Spindle cell neoplasms

A variety of additional diagnoses may enter the histologic differential. Spindle cell neoplasms (melanoma, carcinoma, and dermatofibrosarcoma protuberans [DFSP]) can usually be excluded by clinical presentation and special stains, although DFSP may be CD34 positive and procollagen I dual positive in a manner similar to NSF. NSF, however, does not typically extend into the fat lobules to wrap around individual adipocytes (a feature typical of DFSP).

6. Summary

NSF is a relative newcomer to the world of medicine, having appeared on the scene just over 10 years ago. Strict adherence to a concordant clinical and pathological definition has allowed for careful separation of this entity from other fibrosing disorders, leading eventually to the realization that gadolinium based contrast agents were closely associated with its onset. As planned prospective studies get underway, it is of paramount importance that researchers and clinicians realize that NSF remains a very challenging diagnosis, and that both clinical and histopathological criteria must be employed to reach an absolutely specific diagnosis.

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