Nephrogenic Systemic Fibrosis: An Update and Literature Review

Nefrojenik Sistemik Fibrozis: Güncel Bilgiler ve Literatürün Özeti

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ABSTRACT Nephrogenic systemic fibrosis is a scleromyxedema-like dermopathy characterized by acute symmetric erythematous papules, hardening of the skin, swelling of distal parts of the extremities and nodules. Systemic fibrosis and calcification of organs including skeletal muscle, esophagus, lungs, myocardium and kidney are seen. Majority of cases occur in hemodialysis patients, however the disease may also develop in peritoneal dialysis patients, in patients with renal failure who never have received dialysis and in renal transplant recipients. Histopathological changes vary from a scant proliferation of fibroblasts and minimal collagen production to more florid numbers of fibroblasts and collagen deposition in reticular dermis and subcutis. Antecedent systemic administration of gadolinium-containing contrast agents during magnetic resonance imaging, particularly gadodiamide, is reported in majority of cases. Differential diagnosis includes other diseases presenting with dermal sclerosis (e.g. scleroderma). Among promising treatment modalities are steroids, immunosupression, antihistaminics, plasmapheresis, photopheresis, Uv-A and angiotensin converting enzyme inhibitors. Prevention includes avoidance of gadodiamide in patients with glomerular filtration rate less than 30 mL/min/1.73 m^2 and a careful consideration of risks/benefits of gadolinium-enhanced magnetic resonance imaging. When inevitable, the lowest dose of gadolinium-containing contrast agent possible should be administered and repeated dosing within one week should be avoided. Hydration therapy to favor renal excretion of gadolinium-containing contrast agent is suggested. In stage 4 and 5 chronic renal failure patients, hemodialysis therapy should be considered after gadolinium administration to eliminate the contrast agent.

Key Words: Nephrogenic fibrosing dermopathy; gadolinium; kidney failure, chronic

ÖZET Nefrojenik sistemik fibrozis, akut simetrik eritematöz papüller, ciltte kalınlaşma, ekstremitelerin distalinde kalınlaşma ve nodüllerle karakterize skleroderma-benzeri bir dermopatidir. İskelet kası, özofagus, akciğerler, miyokard ve böbrekte sistemik fibrozis ve kalsifikasyon görülmektedir. Olguların çoğu hemodiyaliz hastalarıdır, ancak hastalık aynı zamanda periton diyalizi hastalarında, hiç diyaliz tedavisi almayan böbrek yetmezliği olanlarda ve böbrek nakli alıcılarında da gelişebilmektedir. Histopatolojik değişiklikler retiküler dermis ve subkütiste az sayıda fibroblast çoğalması ve minimum kollajen üretiminden, daha fazla sayıda fibroblast çoğalması ve kollajen depolanmasına kadar değişiklik gösterir. Olguların çoğunda önceden manyetik rezonans görüntüleme sırasında gadolinyum içeren kontrast ajan -özellikle gadodiamid- kullanımı rapor edilmiştir. Ayırıcı tanı dermal skleroz ile giden diğer hastalıkları (örneğin; skleroderma) içermektedir. Umut vaad edici tedaviler arasında steroidler, immünsüpresifler, antihistaminikler, plazmaferez, fotoferez, Uv-A ve anjiyotensin dönüştürücü enzim inhibitörleri sayılabilmektedir. Korunma önlemleri glomerüler filtrasyon hızı 30 mL/dakika/1.73 m^2'nin altında olan hastalarda gadodiamid kullanımından kaçınılması ve gadolinyumlu manyetik rezonas görüntülemenin zarar/kar oranının dikkatlice gözden geçirilmesini içermektedir. Kaçınılmaz olduğunda, mümkün olan en az dozda gadolinyum içeren kontrast ajan kullanılmalı ve bir hafta içinde doz tekrarından kaçınılmalıdır. Gadolinyum içeren kontrast ajanın renal atılımını desteklenmesi için hidrasyon tedavisi önerilmektedir. Evre 4 ve 5 kronik böbrek yetmezliği olan hastalarda gadolinyum verilmesinden sonra kontrast ajanın atılması için hemodiyaliz tedavisi göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Nefrojenik sistemik fibrozis; gadoliniyum; kronik böbrek yetmezliği

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In 2000, Cowper et al. described a unique scleromyxedema-like dermopathy that developed in 15 renal dialysis patients seen over a period of 3 years.[1] The condition, which they subsequently named as nephrogenic fibrosing dermopathy (NFD), manifested with marked skin thickening/hardening and hyperpigmentation of the limbs and the trunk. Flexion contractures of the upper extremity joints were occasionally associated with the condition.[2] Although the process resembled scleromyxedema, clinical and histopathological features warranted the designation of a new distinct clinicopathological entity. Since its first published description in 2000, NFD has been seen exclusively in patients with renal disease and mostly affects the skin and subcutaneous tissue. Recent reports describing involvement of additional organs and the observation that the disease is mediated by a circulating cell imply that NFD is a systemic disease. Accordingly, a change to the more descriptive name, nephrogenic systemic fibrosis (NSF), was considered to more accurately reflect disease nosology. Other eponyms such as *scleromyxedema-like illness of renal disease*, *scleromyxedema-like illness of hemodialysis*, *scleromyxedema-like fibromucinosis* and *dialysis-associated systemic fibrosis* may also be found in the literature in association with this entity.[3]

EPIDEMIOLOGY

NSF occurs exclusively in patients with preexisting renal insufficiency.[2] The onset of NSF is variable and may occur days, months or years after the onset of renal failure or the start of dialysis.[4] Approximately, 90% of patients with NSF harbor dialysis-dependent chronic renal insufficiency.[2] Rare cases of NSF occur in patients with acute renal failure (e.g. due to obstructive uropathy) or acute hepatorenal syndrome have been reported.[4,5]

Although development of NSF has been ascribed to renal dysfunction from a multitude of factors, it is not likely related to the duration or severity of renal disease. Antecedent systemic administration of gadolinium (Gd)-containing contrast agents, particularly gadodiamide (within 3 months of disease onset) has been increasingly reported in patients with NSF.[2] NSF occurs equally in both sexes, ranging in age from 8 to 87 years old (mean 46.4 years old). There is no race predilection. Cases have been reported in the US and several countries in Europe and Asia.[3]

The etiology of renal disease in patients with NSF is highly variable as well. Neither the etiology, nor the severity of renal dysfunction correlates with severity of NSF. Embolic events, vasculopathy, primary kidney diseases, diabetes mellitus, hypertension, cyclosporine nephrotoxicity and systemic autoimmune diseases have all been reported as causes of renal failure in patients with NSF. The majority of cases occur in patients who have been treated with hemodialysis although the disease may also develop in peritoneal dialysis patients and in patients with renal insufficiency who never has received dialysis. Several cases have been also reported in renal transplant recipients.[4]

CLINICAL PRESENTATION

Clinical features of NSF may include an acute phase that immediately follows exposure to Gd-based contrast media and an overlapping chronic phase characterized by progressive fibrosis. Features in the acute phase are variably present and mimic systemic inflammatory response syndrome: Fever, hypotension, acute kidney injury, anemia, leukoerythroblastic picture, thrombocytopenia or thrombocytosis, leukocytosis, eosinophilia, monocytosis, elevated g-glutamyl peptidase, elevated lipase and elevated D-dimer. Decreased total iron-binding capacity, elevated serum ferritin, low serum albumin and elevated C-reactive protein are invariably present. Because many patients have critical illnesses such as sepsis, acute pancreatitis, hepatorenal syndrome, or acute graft dysfunction that precedes NSF, the acute phase of systemic fibrogenesis may go unrecognized. Onset of the chronic phase is also variable: As early as 4 days or as late as several months after Gd-based contrast media exposure.[6]

SKIN INVOLVEMENT

Patients typically develop acute, symmetric, plaque-like indurations involving the lower limbs and occasionally, the upper limbs, trunk and buttocks.[7]

The primary skin lesions of NSF include symmetric, erythematous papules that coalesce to brawny plaques with an "ameboid" or serpiginous edge. Woody or peau d'orange consistency of the skin is characteristic.[2] Patients often report pruritus, causalgia and sharp pains in the affected areas.[8] Isolated nodules and, rarely, bullae may be seen in conjunction or following the diffuse skin thickening and hardening.[7] In NSF, initial swelling of distal parts of the extremities is followed by thickening, indurations and hardening of the skin in a couple of weeks. The (distal) extremities are the most common areas of involvement, followed by the trunk.[9] The face is almost never involved and sparing of the face is a characteristic feature.[2,9] Stiffening of the hands and flexion contractures also may be seen.[6] Table 1 summarizes the characteristic properties of NSF.

SYSTEMIC INVOLVEMENT

NSF is characterized by systemic fibrosis and calcification involving skeletal muscle, esophagus, lungs, myocardium and kidney. Most patients develop joint contractures and muscle weakness within days to weeks of onset of the disease that may lead to significant immobility in some patients. Patients with NSF have a higher incidence of chronic pulmonary fibrosis, often idiopathic in nature.[2]

Daram et al. reported a case of NSF in a 39-year-old African-American man with end-stage renal disease secondary to hypertension. At autopsy, there was extensive thickened fibrotic skin with plaque-like changes across the upper chest, abdomen and all extremities and bilateral upper- and lower-extremity contractures. Extensive fibrous strands and dense collagenous bands were present throughout the subcutaneous tissue and muscle, including pectoralis, calves, thighs and diaphragm. There was thickening of the parietal and visceral pleura, pericardium, diaphragm, and tunica albuginea. They observed dense fibrous tissue around the great vessels of the heart; dense fibrosis of the left ventricle and septum with mild fibrosis of the right ventricle and mild coronary atherosclerosis. Their examination provided further evidence that there is systemic fibrosis in NSF.[10]

TABLE 1: The characteristic properties of nephrogenic systemic fibrosis.

Acute, symmetric, erythematous papules
Woody or peau d'orange consistency of the skin
Swelling of distal parts of the extremities
Thickening, indurations and hardening of the skin
Distinct nodules
Bullae (rare)
Sparing of the face

PATHOGENESIS

NSF is an acquired disease, yet considered idiopathic and is observed in patients with renal insufficiency, most but not all of whom have undergone dialysis for renal failure. Since its recognition in 1997 and first description in literature in 2000, more than 215 cases have been reported worldwide.[1,9] At present, we have very little information about the precise etiopathogenesis of this disorder.[8] It has been postulated that "a material, possibly a contrast agent, medication or other allergen" might be deposited in the tissues and serve as a surrogate target for circulating fibrocytes.[11] Several "trigger" events have been described that include nontransplant-related surgical procedures, hepatorenal syndrome, vessel trauma (e.g. fistula operation and angioplasty), administration of erythropoietin or angiotensin converting enzyme inhibitors and use of high dose Gd-containing magnetic resonance contrast agents.[2,9] The presence of antiphospholipid antibodies has been demonstrated, but their role in the development of NSF is unclear.[4] It is hypothesized that vessel injury may trigger inappropriate proliferation and activity of circulating fibrocytes leading to deposition of collagen and matrix in the target tissues. Systemic fibrosis, particularly dermal fibrosis, is a hallmark feature of NSF. Circulating fibrocyte, an immunologically unique $CD34^+$ cell, has been found to be the predominant cell population in skin biopsy specimens in patients with NSF. It is hypothesized that NSF results from aberrant traffic and proliferation of circulating fibrocytes, which contribute to marked collagen and matrix deposition in the target tissues, after a yet-to-be-established "immunological trigger".[2]

Erythropoietin has been suspected in the pathogenesis of NSF. Swaminathan et al. observed that patients undergoing dialysis who develop this disorder typically received high doses of erythropoietin before diagnosis, often in the context of acute illness. They suggested that this association may indicate a common etiologic link between erythropoietin resistance and NSF, such as prolonged inflammatory states or development of anti-erythropoietin antibodies. They also speculated that high-level exposure to erythropoietin was an independent contributor to the disease. The expression of CD34 on spindle-like cells in skin affected by NSF suggests infiltration by bone marrow-derived progenitors, which may increase in number by as much 300% after stimulation by erythropoietin. Furthermore, erythropoietin has been shown in vivo to trigger an exaggerated fibrin-induced wound-healing response that is histologically similar to NSF.[12]

Swaminathan et al. presented the data of two patients who had iron mobilization and inflammation after Gd administration. Their data suggested that Gd exposure in patients with renal insufficiency might result in a substantial decrease in total iron-binding capacity and increased iron mobilization, resulting in transferrin oversaturation. They postulated that in some patients, iron mobilization might lead to transmetallation and release of free gadolinium. Free gadolinium and catalytic iron might synergistically coordinate, resulting in oxidative stress, inflammation and tissue injury.[13]

HISTOPATHOLOGY

Although the epidemiological factors and distribution/morphology of the NSF dermopathy are fairly characteristic to permit a clinical diagnosis, the diagnosis is readily confirmed by histopathological examination of a deep skin biopsy specimen, the current standard criterion of diagnosis.[2]

The histological features of cutaneous biopsies vary depending on the age of the lesion. When biopsied early in the disease, the changes may be subtle, with only a scant proliferation of spindled fibroblasts and minimal evidence of collagen production appreciated. Older lesions, however, demonstrate more florid numbers of fibroblasts and collagen deposition in the reticular dermis and subcutis. The subcutaneous septae may be expanded by this fibrotic process. Mildly increased amounts of stromal mucin may also be noted but inflammation is typically absent. $CD34^+$ dermal dendrocytes are abundant, and factor $XIIIa^+$ and $CD68^+$ monocytes and multinucleated cells are found in increased numbers. In early lesions, increased numbers of these cells were also noted. The early infiltration of the dermis by factor $XIIIa^+/CD68^+$ cells may represent a host response to noxious stimuli. In situ hybridization studies of affected skin, muscle and fascia have demonstrated increased expression of transforming growth factor (TGF)-β1 mRNA. It is possible that these dermal dendrocytes may be responsible for the production of this growth factor and the ensuing fibrosis.[11]

A more attractive hypothesis involves bone marrow-derived cells involved in normal wound repair termed circulating fibrocytes.[11] Fibrocytes have a specific immunophenotype and express CD34, CD11b, CD45, HLA-DR, CD71, CD80, CD86, which support their hematopoietic origin. Fibrocytes have been shown to be recruited in response to tissue injury, perhaps endothelial disruption, and they produce inflammatory cytokines, chemokines, growth and angiogenic factors. Fibrocytes are also a source of vimentin, collagen I and III and matrix metalloproteinases. Some reports show extensive hyaluronidase deposition in the papillary dermis in affected patients. Under the influence of various mediators, such as TGF-b, fibrocytes can differentiate into myofibroblasts. Myofibroblasts appear to represent a small proportion of the spindle cells in NSF. Increased levels of TGF-β have been found in the skin and muscle of some affected patients and in association with drugs used in renal therapy. Cutaneous biopsies obtained from NSF patients typically contain no mitotic figures, suggesting that the $CD34^+$/collagen$^+$ fibrocytes that are present arise by recruitment from the circulation and not by proliferation in situ. Further research is ongoing to elucidate the molecular signals that may control fibrocyte

recruitment and trafficking into skin, which may be dysregulated in NSF.[3]

ROLE OF CONTRAST AGENTS

Contrast-enhanced magnetic resonance angiography is often used to evaluate patients with renal failure for transplant eligibility, for visualization of vascular anatomy or for post-transplant complications. Gadodiamide was approved in 1993 for magnetic resonance imaging (MRI) but was not routinely used in patients with chronic renal insufficiency until 1997. Gadolinium-based contrast agents are considered less nephrotoxic than their iodinated counterparts. All Gd-based contrast agents are formulated with excess chelate, because free Gd^{3+} is highly toxic. Of the 5 gadolinium chelates available in the United States, gadodiamide has one of the higher acid dissociation rates and a lower thermodynamic stability. Therefore, this agent must be prepared with a relatively high concentration of chelate to minimize the amount of Gd^{3+} formed in vivo. The half-life of gadodiamide in healthy patients is less than 2 hours, but it can exceed 120 hours in patients with renal insufficiency.[14]

Grobner was the first to suggest a causative role for Gd-containing contrast agents in the pathogenesis of NSF. Five of 9 end-stage renal disease patients developed skin changes 2 to 4 weeks after undergoing magnetic resonance angiography studies. Gadodiamide was the contrast agent used in all patients and all affected patients had metabolic acidosis.[15] Subsequent studies have suggested that NSF is temporally related to systemic administration of gadodiamide in patients with moderate to severe renal insufficiency. NSF developed after a latent period of 2 to 11 weeks; the volume range of gadodiamide used was 9 to 25 mmol (average, 37 mL). Antecedent gadodiamide use has been documented in more than 95% of the patients. Of the 5 FDA-approved Gd agents for MRI studies, 3 agents have been linked to the development of NSF. NSF has been associated with both standard-dose and high-dose Gd administration. The exact role of Gd chelates in the etiopathogenesis of NSF is still being investigated.[2]

Marckmann et al. identified 13 cases of NSF who were exposed to gadodiamide for magnetic resonance arteriography of iliac and lower limb vessels and developed NSF during a 10-month period. Mean age at first sign of NSF was 50 years (range 33 to 66 years). All patients had end-stage renal disease, but they differed with respect to primary renal disease. The median time from gadodiamide exposure to first medically recorded note of clinical signs that were indicative of NSF was 25 days (range 2 to 75 days). The odds ratio for acquiring the disease when exposed to gadodiamide was 32.5. Marckmann et al. did not find an association with acidosis; however, they did not have blood samples from the day of gadodiamide exposure, except in three cases.[16]

Broome et al. investigated 559 magnetic resonance examinations (301 were contrast-enhanced with gadodiamide) performed on 168 dialysis patients during 6-year period. Twelve patients were diagnosed with NSF. All affected patients developed characteristic skin changes 2 to 11 weeks after gadodiamide administration. The odds ratio for development of NSF after gadodiamide exposure was 22.3.[5]

Evenepoel et al. reported two cases of NSF in 2004.[17] The unique and common factor for all of the NSF reports was that most patients had received gadodiamide, with only a few patients who have had other Gd-containing contrast agents (gadopentate or gadoversetamide). Another common feature of most of the affected patients was the high dose of Gd-containing contrast agent used in the patients reported, as most had magnetic resonance angiograms, where two-to threefold doses of Gd-containing contrast agent were needed (0.2-0.3 mmol/kg body weight instead of 0.1 mmol/kg with conventional MRI), a feature of possible relevance in patients with impaired renal clearance.[9]

Boyd et al. reported a case of NSF in a 68-year old female. Her past history was significant for chronic hepatitis C virus infection-induced hepatic failure, for which she received a liver transplant in 1995. Cyclosporine therapy-induced renal failure

necessitated hemodialysis in 2006. Three weeks later, the patient underwent an in-patient MRI heart scan using Gd-containing contrast material. The patient had acidosis, hypocalcemia and hyperphosphatemia, and developed woody indurations on her arms and forearms, calves and shins; a punch biopsy was consistent with NSF. Interestingly, a scanning electron microscopy and energy dispersive X-ray spectroscopy demonstrated Gd only in areas of calcium phosphate deposition in blood vessels.[11]

GADOLINIUM

Gadolinium, with atomic number 64, belongs to the lanthanide series. Non-complexed Gd is unsuitable for clinical use, as it may precipitate and is retained for long periods in the body. Insolubility and toxicity of Gd is largely eliminated by forming either macrocyclic or linear chelates, for example Gd-DTPA (diethylene triaminepentaacetic acid). The biochemical effects induced by Gd salts, for example $GdCl_3$ (Gd chloride), may occur through interference with intracellular calcium-dependent processes and calcium entry into cells. Gadolinium presumably displaces calcium ions from cation-binding sites on cellular membranes and binds to and activates the extracellular calcium-sensing receptor, which is present on various tissues like fibroblasts, kidney, parathyroid glands, hepatocytes and pancreas. $GdCl_3$ can form mineral emboli in the circulation, which are deposited in the capillary bed of organs and are taken up by phagocytosis. Electron-dense deposits found in various organs have been shown to contain Gd and may consist of a complex of Gd and phosphate. Free Gd ion also blocks macrophage function and may cause cell death, which is likely to occur as a result of initial phagocytosis of Gd particles. This process is likely to be mediated by pinocytosis-based internalization. The sequence of events during Gd permeation through the cell membrane into erythrocytes starts with Gd binding to membrane phospholipid, followed by a transfer to membrane proteins and ends with a phase transition in the lipid bilayer and aggregation of membrane proteins that result in the perforation of the membrane.[9]

Intracellular Gd has been recently identified in skin biopsy specimens by using electron microscopy and X-ray spectroscopy. Gadolinium deposits were documented in areas of calcium phosphate deposition in dermal blood vessels. Tissue deposition of intracellular, toxic, free Gd ions may lead to inflammatory reaction with recruitment and increased activity of circulating fibrocytes ultimately resulting in tissue fibrosis. Alternatively, the excess chelate present in certain Gd agents may alter metal homeostasis within the tissues. Interestingly, high concentrations of other metals such as zinc, copper and iron were found in the tissue specimens. It is plausible that in patients with renal insufficiency, a systemic "metallopathy" may exist that may predispose to the development of NSF.[2] It has been speculated that the iron accumulation might possibly result from contamination by the microtome blade itself, but may also be due to iron administration to dialysis patients eventually in large boluses. Deposition of iron in the tissue might be favored by an iron-liberating effect of Gd-chelate with elevation of free serum iron, especially in iron-overloaded patients after Gd-containing contrast media examination. Free iron is highly toxic and, besides other effects, leads to metabolic acidosis and might be an additional cofactor to trigger fibrosis. An interesting hypothesis can be suggested on the role of circulating fibrocytes. These recently characterized blood-borne cells, circulating fibrocytes positive for CD34 and procollagen and involved in wound healing, may invade the dermis and differentiate to dermal cells, resembling functionally and histologically normal fibroblasts, thereby inducing the fibrosing process. Abundance of CD34-positive cells was shown in the specimens and after transmetallation of Gd–chelate complexes, free Gd (and other metals like iron) may be a target for these circulation fibrocytes. Therefore, cutaneous Gd deposition may serve as a nidus for the fibrosing process that leads to the development of NSF.[9]

GADOLINIUM AND END-STAGE RENAL DISEASE

Gadolinium-containing contrast media with a half-life of about 2 hours in patients with normal renal function are almost exclusively excreted by the

kidneys. In patients with deranged renal function, the half-life of these agents is prolonged and may exceed 30 to 120 hours. In addition, gadodiamide, a nonionic low-osmolar Gd agent possesses excess chelate (12 mg/mL). The half-life of gadodiamide is prolonged (34.3 hours) in patients with end-stage renal disease compared with 1.3 hours in subjects with normal kidney function.[2] The delayed excretion of the contrast agent in patients with renal impairment dramatically increases the contact time with the body and thus enhances the risk of biological reactions. Repeated Gd administration, especially of linear compounds, increases the risk of toxicity. Furthermore, nephrotoxicity related to Gd use is directly related to the applied dose of contrast agent in mole.[18]

The majority of patients reported with NSF after contrast MRI studies were administered gadodiamide.[9,18] This may be attributed, to some extent, to the fact that gadodiamide is among the most widely used Gd-containing contrast agents, especially in Europe.[9] Single cases have been reported in the USA and Europe after gadopentetate dimeglumine and gadoversetamide, which both form linear complexes. Macrocyclic agents such as gadoteridol, gadobutrol or gadoterate meglumine are slightly more stable than linear complexes because the Gd^{3+} is caged in a cavity. Linear compounds exhibit more toxic effects after repeated administrations than cyclic compounds, particularly on the reproductive functions and the skin. Further on, a high number of ionic bonds between the ligand and Gd increase the stability of the chelates. Therefore, the dynamic process of Gd release differs from one chelate to another (dissociation kinetic rate e.g., at low pH).[18]

The molecular structure of chelate binding Gd in the case of gadodiamide is also linear. It is a non-tissue-specific and non-ionic low osmolar (780 mOsm/kg) agent. As it is less stable, gadodiamide differs from most other non-tissue-specific extracellular MRI contrast agents by having an excess of chelate. In hemodialysis and peritoneal dialysis patients, half-life is prolonged to 2.6 hour and 52.7 hour, respectively. The Gd excretory rates via hemodialysis measured to be at an average rate of 78.2, 95.6, 98.7, and 99.5% in the first to fourth standard hemodialysis session (i.e. 4 hour sessions every other day, three/week), respectively. In renal failure, there is common evidence of the influence of both metabolic acidosis and absence of adequate clearance of Gd-containing contrast agent.[9]

DIFFERENTIAL DIAGNOSIS

A list of differential diagnoses includes, but is not limited to, scleroderma, scleromyxedema, systemic sclerosis/morphea, eosinophilic fasciitis, eosinophilia-myalgia syndrome, Spanish toxic oil syndrome, scleredema of Buschke, chemical induced fibrosis, fibroblastic rheumatism, amyloidosis, carcinoid syndrome, borreliosis, porphyria cutanea tarda, calcifilaxis and dermatofibrosarcoma protuberans. In early stages, NSF may mimic cellulitis, panniculitis and drug reactions.[3]

Differentiation of NSF from other sclerosing and mucinous deposition disorders is of paramount importance. Scleromyxedema can be differentiated from NSF by the localization of cutaneous involvement and the morphology of lesions. Scleromyxedema typically affects the face and neck with waxy, linearly distributed papules. Unlike scleromyxedema, NSF usually does not include severe systemic manifestations such as myopathy, eosinophilia, arthritis, cerebral symptoms and arteriosclerotic changes in the ocular fundus, kidney and coronary arteries. In addition, IgG-c paraproteinaemia, which is a characteristic feature of scleromyxoedema, is not seen in NSF. NSF differs from systemic sclerosis or the localized variant, morphea, in its morphology, distribution, and histopathology and in lacking autoantibodies. Sclerotic lesions present as ivory-colored plaques, which may involve the face. Patients with systemic sclerosis and CREST syndrome can exhibit a spectrum of findings, such as arthritis, flexion contractures, sclerodactyly and subcutaneous calcification. NSF also can result in flexion contractures; however, sclerodactyly has never been reported in these patients. Mat-like telangiectases on the cheeks and tightening of the nose also are common in scleroderma. Further criteria to distinguish scleroderma from NSF are the

presence of circulating antinuclear antibodies, including anti-Scl-70 or anticentromere antibodies (found in the CREST variant of systemic sclerosis). Eosinophilic fasciitis (Shulmann syndrome) can be distinguished from NSF by its lack of association with renal disease. In addition, eosinophilic fasciitis is usually precipitated by an episode of unusual exertion. Patients usually have a peripheral blood eosinophilia, an increased erythrocyte sedimentation rate and hypergammaglobulinemia. Porphyria cutanea tarda can be excluded by porphyrin studies, and presence of characteristic clinical findings such as bullae, photosensitivity and hypertrichosis. Patients with eosinophila-myalgia syndrome and toxic oil syndrome usually have the history of contaminated substances (L-tryptophan and cooking oil, respectively).[7]

TREATMENT MODALITIES

Although several management strategies including skin-directed and systemic therapies have been described to control or reverse the condition, no definite effective therapy for NSF exists (as of today).[2] Up to now, different treatment modalities have been attempted such as topical steroids, intralesional medications, oral prednisone or other immunosuppressive therapies (Table 2). Most of these treatments have not shown much efficacy, although there are some reports with promising results after treatment by photopheresis and ultraviolet-A radiation. Case reports have shown good responses to extracorporal photopheresis in patients with NSF. Extracorporal photopheresis has been previously adopted in other sclerosing diseases such as scleroderma, scleromyxoedema and eosinophilic fasciitis with successful results. Angiotensin-converting enzyme inhibitors have been suggested, due to their inhibiting effects on TGF-β. High-dose intravenous immunglobulin may be an effective treatment for patients with NSF.[7] There have been anecdotal reports of patients showing some response to thalidomide.[3] The current best possible way to treat the condition is by early restoration of renal function, mostly by renal transplantation.[2]

TABLE 2: Promising treatment modalities for nephrogenic systemic fibrosis.

Steroids (topical/oral)
Immunosupressive agents (tacrolimus, cyclosporine)
Intralesional therapies (triamcinolone/methotrexate/interferon-alpha)
Selective antihistaminics (cimetidine and ranitidine)
Intravenous immunglobulin
Plasmapheresis
Photopheresis
Localized psoralen + ultraviolet A
Angiotensin converting enzyme inhibitors

PREVENTION STRATEGIES

In patients with moderate or severe renal insufficiency, it is advisable to avoid Gd agents, particularly gadodiamide. MRI studies without Gd administration or alternative imaging techniques may be considered to answer the clinical question. In scenarios where the benefits of the Gd-enhanced MRI examination far outweigh the risks, use of lowest possible dose of Gd is recommended. Patients with renal insufficiency who receive Gd agents may benefit from a prompt hemodialysis, preferably within 3 hours of Gd administration. The patients with renal insufficiency who receive Gd agents should be periodically monitored for symptoms and signs of NSF. Early, accurate diagnosis and prompt restoration of renal function are beneficial in patients with NSF.[2]

Definition of serum creatinine and calculation of estimated glomerular filtration rate is recommended for patients bearing an increased nephrotoxic risk and for all patients with a history of chemotherapy, blood or connective tissue disorder or a "pro-inflammatory" disease (major surgery, vasculitis, thrombosis, systemic infection, liver cirrhosis, acidosis) within 6 months prior to the examination. Further renal risk factors such as advanced age (> 70 years), suspected or known renal diseases, diabetes mellitus, arteriosclerosis, peripheral vascular disease, congestive cardiac failure, nephrotoxic medication (contrast load in the previous 72 hours, diuretics, NSAID, aminoglycosides, amphotericin, cyclosporine A), hyperuricemia and history of dialysis must be assessed.[18] Most recently, official authorities have considered administration

of gadodiamide to be contraindicated in patients with a glomerular filtration rate less than 30 mL/min/1.73 m^2 as well as in liver transplant recipients.[9] Although authorities did not discriminate between different Gd preparations at all, they recommend a careful consideration of risks and benefits of MRI with Gd-containing contrast agents and advise to choose alternative imaging methods whenever possible. When inevitable nevertheless, the patient has to be informed and MRI should be performed with the lowest dose of Gd-containing contrast agent possible (0.1 mMol/kg bw), only after correction of acidosis and exclusion of iron overload, and repeated dosing within a time frame of one week should be avoided.[9,18] Additionally, Gd should be avoided if ever possible in case of known allergies to any Gd contrast agent and known or diagnosed NSF.[18] Again, not evidence based, in stage 3 kidney patients, an approach could be chosen comparable to conventional iodinated contrast media, namely hydration with 1 mL/kg body weight/h of 0.9% saline solution 12 hour before to 12 hour after the MRI examination to favor renal excretion of the Gd-containing contrast agent. In stage 4 and 5 patients, performance of up to four hemodialysis sessions should be considered after Gd administration to eliminate the Gd-containing contrast agents.[9] More stable Gd complexes should be preferred. It is important to underline the fact, that most Gd complexes may still be used in case of terminal renal insufficiency, but the risk/benefit ratios must directly be compared to the application of computed tomography with iodinated contrast media.[18]

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