
Nephrogenic fibrosing dermopathy nfd: A novel clinical entity in patients with renal disorders

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NFD is a newly recognized phenomenon , occurring only in the context of renal dysfunction , featuring excessive skin fibrosis with unique distribution of the involved areas including the extremities and trunk and sparing the face and neck. The fact that the fibrotic process of NFD extends beyond the skin , displaying an evidence of systemic involvement prompted the name of the disorder to be changed to NSF . In the published literature NFD and NSF has been used interchangeably . The new nature of the disease makes it hard to make generalizations , however the available epidemiological data revealed that the disease affects male and female equally , with no racial predilection , striking mainly the middle-aged patients with a mean age of 46.4 years. The underlying mechanisms of the enhanced fibrogenesis in (NFDNSF) are still elusive, prompting multiple aetiological hypotheses, which are at best speculative. Nevertheless, the cause seems to be multifactorial , requiring the active interplay of : low GFR , GD exposure, endothelial dysfunction, stimulated haematopoietic environment , systemic inflammation , and hyperparathyroidism as key elements of promoting the fibrogenesis into motion . Renal dysfunction , with or without renal replacement therapy, is the most important single factor that predisposes patients to , and initiates the sequence of events of (NFDNSF) . Neither the duration nor the cause of renal dysfunction seems to alter the pathogenetic series . Unfortunately , the exact degree of GFR that sets for (NFDNSF) has not been precisely determined yet . Besides the striking epidemiological association between gadolinium exposure and (NFDNSF) development , the detection of gadolinium in tissue biopsies sampled from lesions , strengthened the NSF/GD link , and revealed the mysterious nature of the trigger that sets for (NFDNSF). Endothelial dysfunction encountered in the setting renal disease , primes for other adverse vascular events including : hypercoagulable state, vascular thrombosis and injury , and release of vasoactive profibrotic and inflammatory cytokines that contribute to the fibrotic burden of (NFDNSF) . High erythropoietin levels enhance endothelial dysfunction and inflammation, as well as stimulates cell proliferation and wound healing response , however the exact role of epo in (NFDNSF) remains controversial. Circulating Fibrocytes (cF) , the cells that are normally involved in wound healing and tissue remodeling, are believed to be the incriminated cells responsible for this widespread cutaneous and systemic fibrosing process . The mechanism by which Gd induces the aberrant activation and recruitment of circulating Fibrocytes (cF) into skin and tissues remains to be

elucidated , however , in the setting of renal dysfunction , the instability of Gd - by transmetallation in which catalytic iron , systemic inflammation and oxidative stress play a central role –as well as reduced Gd clearance –which prolongs tissue exposure to Gd – together with endothelial dysfunction –which allows easy Gd access into tissues - , all may stand for stimulation of circulating Fibrocytes .Once in tissues , macrophages phagocytose (Gd3+) and Gd3_ containing macrophages produce profibrotic cytokines that act locally and attract cF, which promote the fibrotic Response (Perazella , 2007).On cellular basis , the persistence of fibrosis is explained by the "persistently activated fibroblast phenotype" concept even after the removal of the original trigger .Clinically , patients with NFD complain of swelling , thickening , hardening of the skin of involved areas , some patients experience pruritis , burning pains over the lesions ,as well as muscle weakness and deep bony aches .On examination , cutaneous lesions start as generalized oedema with plaque-like erythematous rash , progressing to induration , altered pigmentation and loss of skin appendages giving a "peau d orange" appearance .NFD has a tendency for symmetrical affection of the dependent parts of the body and high blood-flow areas , striking the lower extremities ,the upper extremities and trunk ,respectively .A full-thickness skin biopsy from involved areas is the gold standard for establishing diagnosis of (NFDNSF) .Characteristic histological findings of NFD include : thickened collagen bundles , excessive mucin deposition and proliferation of fibroblasts and elastic fibers.The cell populations and fibrotic elements of skin biopsies vary depending on the age of the lesions .The unique features of NFDNSF including : the specific distribution of cutaneous involvement with facial sparing , the occurrence in the setting of renal failure , temporal relation to gadolinium exposure and the unique histopathologic features (i.e. thickened collagen bundles with surrounding clefts, mucin deposition and a proliferation of fibroblasts and elastic fibres with lack of inflammatory cells on biopsy) and its specific immunophenotype profile , distinguish NFD from the other sclerotic and panniculitic cutaneous conditions seen in patients with end-stage renal disease (Perazella , 2007).The prognosis depends on the extent , severity , and rapidity of cutaneous involvement as well as the extent of systemic involvement .Recommendations for prevention of NSF rely on addressing the risk factors .For the time being, it is best to avoid administration of Gd3 to patients with AKI and stage 3/5 CKD (including transplant patients) and those who are on dialysis.Because radiocontrast induced nephropathy is generally reversible and NSF is not, exposure to radiocontrast with standard prophylaxis is probably preferable (Perazella,2007).In patients who are on hemodialysis, GBCM should be administered only if the benefits of obtaining a contrast-enhanced magnetic resonance image substantially outweigh the risk. At the completion of imaging, patients should go to the hemodialysis unit for initiation of dialysis, and dialysis treatment should be administered for 3 consecutive days (Swaminathan and Shah 2007). Because peritoneal dialysis clears Gd3 inefficiently, GBCM is absolutely contraindicated in these patients , temporary hemodialysis if exposure occurred may be a consideration (perazella ,2007).correction of other potential risk factors including : reducing dosages of EPO and iron enough to achieve target hemoglobin level , control of PTH levels , and limiting systemic inflammation , is likely to help prevention of NSF .Many different

treatment options have been explored for NFD/NSF, with varying degrees of success. No single treatment has been proven effective, however, improvement in renal function seems to halt or reverse the process (Weiss et al., 2007). Investigational therapies that show objective improvement in the setting of worsening or stable chronic renal failure should be targeted for further investigation. Therapeutic approaches that have shown promise in NFDNSF include: pentoxifylline (Cowper et al., 2006), plasmapheresis (Hubbard et al., 2003), photodynamic therapy (Schmook et al., 2005), UVA-1 phototherapy (Kafi et al., 2004), extracorporeal photophoresis (Lauchli et al., 2004) and sodium thiosulphate (Yerram et al., 2007)..