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Henoch-Schönlein Purpura Nephritis

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Henoch-Schönlein purpura (HSP) is a systemic vasculitic disorder first reported by Heberden in 1806. The association of purpura and joint pain was described by Schönlein in 1837, who termed it "peliosis rheumatica." Henoch added a description of four children with skin lesions associated with colicky abdominal pain, gastrointestinal hemorrhage, and joint pain in 1874, and in 1899 pointed out that renal involvement sometimes occurred. Synonyms include anaphylactoid purpura, allergic vasculitis, leukocytoclastic vasculitis, and rheumatoid purpura. It is a multisystem disorder mainly affecting the skin, joints, gastrointestinal tract, and kidneys but sometimes other organs.

It has been suggested that IgA nephropathy, first described by Berger and Hinglais, and HSP represent a spectrum of clinical presentations of the same or a similar disorder, the former lacking the clinical manifestations in extrarenal organs seen in the latter.

Pathogenesis

The pathogenesis of HSP remains unknown; however, it is generally considered to be an immune complex-mediated disease characterized by the presence of polymeric IgA1 (pIgA1)-containing immune complexes predominantly in dermal, gastrointestinal, and glomerular capillaries (1–3). The pathognomonic granular IgA and C3 deposits in the mesangium are indistinguishable from those seen in IgA nephropathy. Similar immunohistologic findings have also been observed in the kidneys of patients with liver cirrhosis, dermatitis herpetiformis, celiac disease, and chronic inflammatory disease of the lung.

Biology of IgA

In healthy subjects, IgA is found abundantly in mucosal fluids, but its concentration in the serum is relatively low. IgA in primates occurs as two isotypes, IgA1 and IgA2, which are distinguished by the presence in IgA1 of a hinge region containing 5 *O*-linked oligosaccharide side chains composed of serine-linked *N*-acetylgalactosamine (GalNAc) and galactose, the latter of which may be sialylated. Sixty percent of IgA in secretions is of the IgA2 subclass, is primarily polymeric, and has a secretory component synthesized by glandular epithelial cells. Serum IgA is mostly IgA1 and is 90% monomeric. In HSP nephritis, mesangial deposits contain predominantly pIgA1 with bridging J protein, the secretory component being absent (4,5).

Site of pIgA Production and the Roles of Impaired IgA Synthesis and Clearance

Both increased IgA synthesis and diminished clearance have been implicated in the pathogenesis of IgA immune complex deposition. Increased pIgA production by the mucosal immune system in response to a mucosally presented antigen has been hypothesized as a potential mechanism for the development of HSP (6,7). Hyper-reactivity of both B and T cells in response to specific antigenic stimuli *in vitro* has been reported in patients with IgA nephropathy and HSP (8). Clinical observations *in vivo* have implicated infectious antigens as immunomodulators, and there are clinical associations between mucosal infections and HSP (Table 1). Other antigens, including dietary proteins (gliadin) and extracellular matrix components (collagen and fibronectin), have also been implicated. No exogenous antigen has been identified consistently either in circulating immune complexes (CIC) or in the mesangial deposits (6–10). Some studies have demonstrated increased pIgA production in mucosal and tonsillar cells, whereas others have unexpectedly shown a downregulation of pIgA production in the mucosa and upregulation in the bone marrow (1,5). Altered mucosal pIgA production allowing increased antigen penetration to stimulate an exaggerated marrow response has been suggested (5). Some authors have suggested that the deposited IgA is a rheumatoid factor (11). Total serum levels of IgA are increased in 40 to 50% of patients with HSP, with elevations in both monomeric IgA and pIgA (7,12,13). There also may be impairment in the binding of IgA1 to the hepatic asialoglycoprotein receptors, which facilitates the physiologic clearance of IgA from the circulation, thereby impairing clearance in patients with IgA nephropathy and HSP (1,14).

Mechanism of Mesangial IgA Deposition

Capillary IgA immune complexes are likely the result of either CIC deposition or *in situ* complex formation. There is reasonable clinical evidence to suggest that CIC deposition is an unlikely sole explanation. First, IgA mesangial deposits are present despite the absence of demonstrable IgA-containing CIC in 50% of patients (15,16). In addition, the high circulating IgA level is in itself insufficient to produce mesangial IgA

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Table 1. Antigens implicated in the precipitation of HSP

Infections
upper respiratory tract infections, measles, rubella, human parvovirus B19, mycoplasma, Coxsackie virus, toxocara, amebiasis, salmonella hirschfeldii, clostridium difficile, morganella morganii, streptococcus, mumps, tuberculosis, legionella longbeachae, helicobacter pylori, adenovirus
Medications
vancomycin, ranitidine, streptokinase, cefuroxime, diclofenac, enalapril, captopril
Miscellaneous
leukemias and lymphomas, breast cancer, small cell lung cancer, myelodysplastic syndrome, autosomal recessive chronic granulomatous disease, exposure to cold, food hypersensitivity

deposits. This is demonstrated by the absence of mesangial IgA deposits in most patients with HIV infection despite high circulating levels of polyclonal IgA in some, and similarly an absence of mesangial deposits in most patients with IgA myeloma despite the presence of the circulating paraprotein. As a result of these observations, alterations in the biochemical properties of IgA were sought as a potential mechanism that might facilitate IgA deposition in capillaries. Serum IgA1 has been shown to be abnormally *O*-glycosylated in patients with HSP and IgA nephropathy (1,14,17,18). Circulating IgA1 has reduced terminal galactose on *O*-linked sugars, and a B cell defect in β-1,3-galactosyltransferase has been implicated (1,14). Altered hinge region glycosylation may change IgA1 structure, modifying interaction with matrix proteins, IgA receptors, and complement, causing mesangial deposition and subsequent injury (1,14). A study demonstrating abnormal IgA glycosylation restricted to those HSP patients with clinical nephritis lends support to a role for altered IgA1 *O*-glycosylation in the pathogenesis of IgA-associated glomerular disease. The presence and potential pathogenetic role of circulating IgA-antineutrophil cytoplasmic antibodies (ANCA) and IgA rheumatoid factors observed in patients with HSP have also been reported.

Pathogenesis of Glomerular Injury

Traditional mediators of inflammation are implicated in glomerular injury. Deposition of C3 and properdin without C1q and C4 are typical, suggesting alternate pathway activation. Despite the demonstration of complement components in skin and renal biopsy, there remains controversy regarding the role of complement in the pathogenesis underlying HSP. Some authors believe that IgG co-Ig deposition may induce complement activation and modulate disease activity (4,19). The role of cytokines, growth factors, chemokines, and adhesion molecules in mesangial proliferation are under investigation. Interleukin-1 (IL-1), IL-6, platelet-derived growth factor, tumor necrosis factor, free oxygen radicals, prostanoids, leukotrienes, vascular cell adhesion molecule-1, membrane attack complex (C5b-9), and a circulating immunostimulatory protein (90K) have all been implicated.

Relationship between HSP and IgAN

The relationship between IgA nephropathy and HSP remains obscure, since the pathogenesis of both are still enigmatic despite the considerable information presented. However, a good deal of evidence suggests that the two disorders are pathogenetically linked. Many (but not all) patients with both disorders have increased serum IgA levels (7,12,13) and IgA-containing CIC (12,19). Other observations in favor of a hypothesis of commonality include the indistinguishable nature of the renal histopathologic lesion (20), the presence of clinically silent but histologically detectable IgA deposits in dermal and gastrointestinal tissue in patients with Berger's disease (21,22), and the occasional report of HSP occurring in patients with prior long-term IgA nephropathy (23). Finally, one of two identical twin brothers simultaneously infected by proven adenovirus developed severe HSP nephritis progressing to chronic renal insufficiency, while the other developed Berger's disease with recurrent asymptomatic hematuria (20).

Pathology

Light Microscopy

The pathology of HSP is inconstant, with varying glomerular proliferation and cell infiltrates between patients and during the course of the disease in a single patient (24). There are two main classification schema for renal pathologic changes in HSP nephritis (25,26), with other less well-documented systems and modifications (24,27,28). The first described primarily uses the degree of mesangial hypercellularity (25). In this classification, grade I is the most benign and least frequent lesion, involving only 2% of biopsies, with minimal glomerular changes. Grade II, or mesangial proliferative or mesangiopathic glomerulonephritis, is characterized by a mild increase in mesangial cellularity with or without a few circulating leukocytes and generally no crescent formation, and occurs in 10 to 32% of biopsies. Grade III, or focal and segmental glomerulonephritis, also termed focal segmental endocapillary proliferation, is the most common abnormality, found in 20 to 45% of patients biopsied (Figure 1A). It consists of focal and segmental moderate mesangial hypercellularity, often with segmental capillary luminal leukocytes and scattered capillary wall fuchsinophilic deposits. Grade IV, diffuse proliferative glomerulonephritis, also called diffuse endocapillary proliferation, is characterized by extensive mesangial proliferation, variable intraluminal leukocytes, and up to 50% crescents. Grade V is more severe diffuse proliferation with more than 50% crescents. The diffuse lesions are observed in 15% of biopsies. A second histologic classification, developed by the International Study Group of Kidney Disease in Childhood, uses crescents as a critical factor (26). In this schema, grade I has minimal alterations, grade II is pure mesangial proliferation, and grades III to V have focal segmental or diffuse proliferation with $<$50%, 50 to 75%, or $>$75% crescent formation, respectively. Grade VI has glomeruli with a membranoproliferative pattern of injury, found in 2% of biopsies.

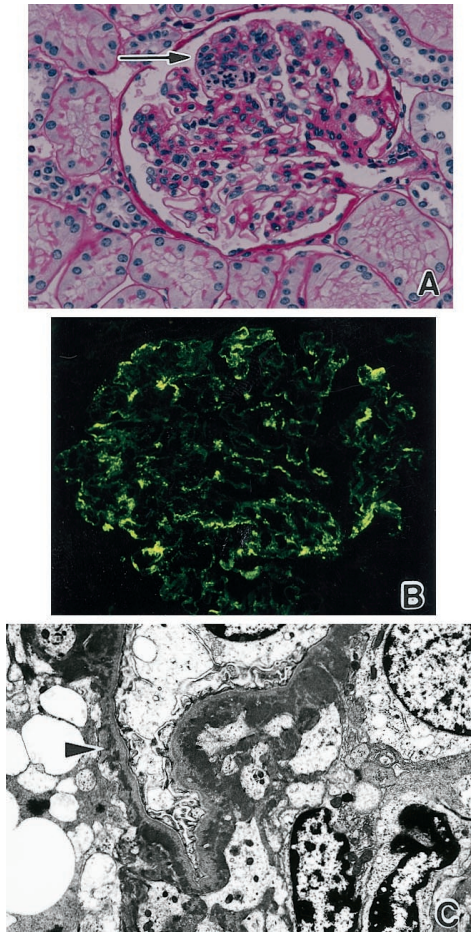

Figure 1. (A) Light microscopy. The glomerulus shows focal and segmental mesangial hypercellularity with associated capillary luminal leukocytes (arrow). Periodic acid-Schiff stain. (B) Immunofluorescence microscopy. There is granular staining for IgA in mesangial regions and segmentally along capillary walls. (C) Electron microscopy. There are electron-dense deposits in the mesangium (arrow), and segmentally in subendothelial locations (arrowhead). Magnification: ×150 in A; ×160 in B; and ×3250 in C.

Crescents were considered in this schema as they significantly affect symptomatology and long-term outcome. Forty percent of patients biopsied have crescents, 80% of these with <50% of the glomeruli involved. The remaining biopsies have 50 to 75% of the glomeruli showing crescents, and only rarely are 75 to 100% of glomeruli involved. Patients with focal or diffuse proliferation and >50% crescents in an initial biopsy have worse outcomes. The degree of tubulointerstitial injury correlates with the glomerular pathology. Renal morphology in HSP cannot be distinguished definitively from that in IgA nephropathy, as the glomerular lesions are similar and vasculitis is virtually never observed within the kidney (29).

Immunofluorescence Microscopy

The characteristic and diagnostic finding is granular mesangial IgA, which is often accompanied by C3, fibrinogen, and both light chains, and less frequently by IgG and/or IgM (24,28). In more proliferative lesions there may be more intense staining, often with segmental IgA in capillary walls (Figure 1B). Fibrinogen is in the urinary space when crescents are present.

Electron Microscopy

Electron-dense deposits are within mesangial regions, and often are small and scattered throughout the mesangia (Figure 1C). In more active disease, there may be larger and more numerous mesangial deposits with capillary wall involvement, including small subendothelial and scattered small-to-large "hump"-shaped subepithelial deposits. There are variable visceral epithelial cell foot process effacement and capillary basement membrane thinning, thickening, and lamellation depending on the degree of glomerular injury.

Clinical Features

Although HSP can occur at all ages, it predominantly affects children younger than 10 yr of age, and has a 2:1 male preponderance (25,30,31). It has a wide geographic distribution and is more prevalent in the winter months (25,31). It is generally a benign, self-limited disorder that follows an intercurrent illness, usually of the upper respiratory tract (25,30–32). It may also be precipitated by other infections, medications, or miscellaneous conditions (Table 1). In one cohort analysis of 219 patients, a potential eliciting factor, mostly infectious, was identified in 37% of the cases (18). Although it can affect all ethnic groups, it is reportedly uncommon in those of African descent (33).

The classic clinical symptoms include purpuric rash, abdominal pain, arthralgias, and hematuria**,** but the spectrum of the expression of HSP may vary from only minimal petechial rash to severe gastrointestinal, renal, neurologic, urologic, pulmonary, and joint disease. There is age-related organ severity with a prevalence of skin involvement in children, and kidneys in adults (25,30,31).

Genetic Factors

Susceptibility to HSP may have a genetic origin. Several reports suggest that deficiency of complement 4 (C4) from deletion of C4 genes predisposes patients to IgA nephropathy and HSP nephritis (34). Japanese patients with HSP reportedly have a higher prevalence of complement C4 gene deletions than control subjects (34,35), but this has not been observed in unrelated populations from Italy, Spain, Kentucky, or the mid-Southern United States (36). The DQA1*301 gene has been implicated in one study (37). In another study it was demonstrated that the presence of DRB1*01or DRB1*11 may facilitate disease onset, while DRB1*07 was shown to induce resistance to the disease (38). It has been suggested that the IL-1 receptor antagonist (IL1RN*2) allele might be a genetic marker shared by patients with HSP nephritis and a group of IgAN patients with recurrent gross hematuria (39). In a group of Swedish patients, the presence of HLA B35 (and possibly HLA B18) has been postulated to predispose to recurrent disease (40). The influence of deletion polymorphism of the angiotensin-converting enzyme gene on the progression of

nephropathy and on proteinuria has been suggested, but studies have yielded conflicting results (41,42).

Extrarenal Manifestations

Extrarenal involvement often lasts more than a month and its outcome is almost always favorable.

Dermal. The dermal lesions are the most distinctive and characteristically involve the extensor surfaces of the lower extremities and buttocks in a symmetric manner, although involvement may be more extensive. The lesions originate as erythematous macules, which develop into purple, nonblanching, nonpruritic, urticarial, purpuric papules, which in severe cases may become confluent. Skin biopsies of the lesions demonstrate leukocytoclastic vasculitis. There may be associated edema of the hands, feet, or face. The rash may rarely present as hemorrhagic vesicles and bullae and desquamation may occur (30,32). Localized edematous swelling of the subcutaneous tissues of the lower extremities and hands is frequently observed and does not correlate with the presence or degree of proteinuria (30,31). Swelling of the scalp, ears, or periorbital region may occur less often (30,31).

Gastrointestinal. Gastrointestinal involvement occurs in approximately two-thirds of the cases of HSP, is usually manifested by abdominal pain (32,43), and symptoms precede the rash in 14 to 36% of patients (43,44). Vomiting, diarrhea, periumbilical pain mimicking appendicitis, and bloody stools are the main abdominal symptoms (44). Major gastrointestinal complications develop in about 5% of patients, of which intussusception is the most common (43). Bowel ischemia and infarction, necrosis, intestinal perforation, fistula formation, late ileal stricture, acute appendicitis, massive upper gastrointestinal hemorrhage, pancreatitis, hydrops of the gallbladder, and pseudomembranous colitis are seen infrequently (43,45). In the past it was not uncommon for patients with HSP presenting with an acute abdominal syndrome to undergo unnecessary laparotomy (43,44). The use of ultrasonography has in recent years proved valuable in diagnosing intra-abdominal pathology in these patients, and is sensitive in distinguishing bowel wall edema, bowel dilation, ascites, ileus, and intussusception. Serial ultrasonography and/or computed tomography scanning have permitted a more conservative approach, with the avoidance of unnecessary surgery. Color Doppler ultrasonography may be a useful adjunct to gray scale in demonstrating blood flow signals in diseased bowel wall. The most common indications for surgical intervention include intussusception, perforation, necrosis, and massive gastrointestinal bleeding (45).

Joint Involvement. Two-thirds of patients experience self-limiting arthralgias and periarticular edema, which may be the presenting symptom. Synovial effusions are absent, and the knees, ankles, elbows, and wrists are mainly affected (25,30,31).

Unusual Extrarenal Features. Rare complications that have been reported include esophageal stenosis, hemorrhagic pancreatitis, protein-losing enteropathy, pulmonary function abnormalities, pulmonary and pleural hemorrhage, thrombocytosis, ureteral obstruction, neurologic complications including encephalopathy, cortical blindness, seizures, intracerebral hemorrhage, headache, electroencephalogram changes, cerebral vasculitis and behavioral changes, urologic manifestations including scrotal swelling, cord hematoma, signs and symptoms mimicking cord or hydatid torsion, testicular pain, painful ecchymotic induration of the scrotum, testicular necrosis, renal hemorrhage, hemorrhagic ascites, and hemorrhagic cystitis.

Renal Involvement. Renal involvement is a common, but inconstant manifestation of HSP, and its incidence varies with the population studied (31,46). Rieu and Noel reported renal involvement in 33% of children and 63% of adults with HSP (47). In one series, HSP was the commonest cause of crescentic glomerulonephritis in children (48). A characteristic feature is hematuria that most often is macroscopic but may be microscopic and either transient, persistent, or recurrent. Hematuria may accompany relapses of purpura or recur long after the extrarenal manifestations have resolved, often in association with upper respiratory infections (31,46). Usually, there is associated proteinuria of variable intensity, and the frequency of the nephrotic syndrome is also extremely variable. Deterioration of GFR may occur, and azotemia or end-stage renal failure may ensue (31,46). There is controversy over whether there is a correlation between the intensity of the extrarenal manifestations and the severity of the nephropathy (18,25,31).

Diagnostic Investigation

There is no specific serologic test to diagnose HSP. Elevated levels of IgA, IgA-rheumatoid factor, and IgA-containing immune complexes have been detected in patients with HSP (7,12,13), and although a correlation between serum IgA levels and clinical features has been suggested, it has not been demonstrated consistently (4,10). The diagnosis is made on the basis of clinical suspicion, and laboratory tests are directed mainly toward excluding other diagnostic possibilities and assessing the extent of renal involvement. Renal biopsy is especially useful in distinguishing HSP from other disorders and, for patients with renal disease, in assessing prognosis and suggesting the need for treatment. Plasma levels of C3a and C4a provide a sensitive indicator of *in vivo* complement activation and have been suggested as a monitor of disease progression (49). IgA ANCA have been reported in patients with HSP and IgA nephropathy by some (50,51), but not by others (52). One group reported reactivity with a novel 51-kD membrane-associated antigen distinct from myeloperoxidase and proteinase 3 (51). Rarely, IgG ANCA has also been reported (53). Severity and persistence of proteinuria have been demonstrated to be the most accurate clinical predictors of the eventual course (54,55), thereby mandating urine testing in every case. In one study, increased plasma levels of thrombomodulin, tissue type plasminogen activator, and plasminogen activator inhibitor-1 were demonstrated in patients with HSP (56).

Course and Prognosis

The average duration of the disease is 1 month, even though it may run a protracted course over several years and there is a tendency for recurrences. Successive episodes of purpura are

common during the first weeks of disease but rarely occur beyond the third month. A single attack seldom lasts more than 1 week, and attacks of purpura are associated inconstantly with exacerbation of renal symptomatology (31,46). Although the disease is usually self-limited with a good eventual outcome, the glomerulonephritis associated with HSP may uncommonly lead to renal failure (31,46,57). For that reason, persistent proteinuria should probably be aggressively treated with angiotensin-converting enzyme inhibitors in patients with HSP.

Prognostic Factors

Age. The disease in children is milder, of shorter duration with fewer recurrences, and with significantly fewer renal and gastrointestinal manifestations (25,30,31). Renal involvement with transient hematuria without renal functional impairment is much more frequent in children than in adults (18). When renal signs result in the need for a renal biopsy (*e.g.*, if urine protein exceeds 1 g/d and/or renal insufficiency is present), the risk of developing chronic renal failure is approximately 18% in children and 28% in adults (47,58). A retrospective study of 162 patients with HSP found that adults had more frequent and severe renal involvement, and required more aggressive therapy with steroids and/or cytotoxic agents. The final outcome was relatively good in both age groups, with complete recovery in 93.9% children and 89.2% adults (59).

Presenting Symptoms. While patients who present solely with microscopic hematuria generally have complete renal recovery, those with either an acute nephritic syndrome or proteinuria greater than 1 g/d at onset do worse, particularly if they develop the nephrotic syndrome (46,47). Macroscopic hematuria is associated with a high likelihood of crescents on renal biopsy and worse renal function (60). Severe abdominal symptoms, persistent purpura, and age at onset of more than 7 years were shown to be significant risk factors for renal failure according to one study (61).

Histology. The most accurate prognostic factors are histologic. Percentage of crescents, the presence of interstitial fibrosis, and extension of mesangial deposits to include dense subepithelial deposits are correlated with the risk of chronic renal failure (47,62). The risk is highest in children with crescents in more than half of the glomeruli (47). In adults even fewer than 50% crescents augurs an unfavorable course. The course of persistent renal sequelae and further renal flare-ups cannot be precisely predicted by histology, and long-term follow-up is warranted (47,62).

Pregnancy. The effect of pregnancy on the course of this syndrome remains unclear. Exacerbations with oral contraceptives and menses, and remission during pregnancy have been reported, although this appears to be unusual (63). Treatment remains symptomatic. Hypertension, proteinuria, and renal function may worsen (64–66).

Management

The extrarenal manifestations of the disease are managed by appropriate symptomatic measures. Severe skin lesions may require oral corticosteroids, which may also improve abdominal pain (44) and protein-losing enteropathy (67). Severe gastrointestinal complications may occasionally require surgical intervention (45). The treatment of HSP nephritis is controversial, and recommendations are based on small, often uncontrolled series.

Steroids

The majority of patients have either no clinical renal involvement or have microhematuria, mild proteinuria, and normal renal function. These patients do not require steroid therapy, and the disorder is usually managed symptomatically. An uncontrolled prospective study of 38 children with severe forms of HSP nephritis suggested improvement in activity and chronicity indices on renal biopsy after the administration of methylprednisolone pulse therapy (68). Another study seemed to verify that early administration of prednisone may be useful in preventing the development of nephropathy in HSP (69). One group suggested treating patients with risk factors for renal involvement with corticosteroids at the onset of disease (61).

Multidrug Therapy

A prospective study of 12 patients with HSP who presented with rapidly progressive glomerulonephritis suggested benefit from intensive multidrug therapy. In this protocol, methylprednisolone, cyclophosphamide, dipyridamole, and prednisone were used (70). Clinical improvement with combined corticosteroid and azathioprine therapy is suggested by another study of 21 children with severe HSP nephritis (71). According to one group, prednisone and cyclophosphamide induced and maintained a complete remission in seven of eight patients with biopsy-proven HSP nephritis (72). Another uncontrolled study showed benefit from a regimen of prednisolone, cyclophosphamide, heparin/warfarin, and dipyridamole in patients with HSP who had severe glomerular histologic changes (73).

Miscellaneous

The use of intravenous Ig (IVIg) for the treatment of HSP is anecdotal. It has been advocated as effective treatment for abdominal pain (74) and other gastrointestinal symptoms (75). In one study of 11 adults, high-dose IVIg reduced proteinuria, hematuria, leukocyturia, and the histologic index of renal disease activity (76). The same group demonstrated the efficacy of low-dose IVIg for moderate IgA nephropathy and HSP (77). The clinical courses of nine children with a rapidly progressive type of HSP nephritis demonstrated that plasmapheresis instituted early in the course of the disease might have been an effective sole therapy in improving prognosis (78). A retrospective investigation of 13 patients suggested that urokinase may prevent the mesangial proliferation associated with IgA nephropathy and HSP (79).

HSP Nephritis and The Renal Allograft

HSP nephritis may recur after transplantation (80,81), and recurrence rates are increased in recipients of living-related transplants (82). Meulders *et al.* report the actuarial risks for renal recurrence and for graft loss due to recurrence to be 35 and 11% at 5 years after transplantation, respectively. Recur-

rence seemed to be associated with a shorter duration of the original disease, occurred despite a delay of more than 1 year between disappearance of purpura and transplantation, and was not prevented by a triple immunosuppressive regimen that included cyclosporin (80). Kessler *et al.* reported a retrospective study of 84 patients who underwent renal transplantation for ESRD secondary to IgA nephropathy or HSP and reported no reduction in incidence or severity of IgA recurrence with cyclosporin compared to that observed with immunosuppressive regimens which excluded it (81). In most patients, no clinical manifestations or only mild disease accompanies histologic recurrence in allografts (83).

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