study, acidosis induced with acetazolamide treatment resulted in the appearance of B2 in the apical membrane of α-intercalated cells, suggesting that another H^+-ATPase or an H^+-ATPase that includes both B1 and B2 can be recruited to the plasma membrane when assembly of the holoenzyme is stressed.[13]

Intercalated cells are highly dynamic and can rapidly respond to the signals induced by systemic acid/base changes to reduce or increase their rate of vectoral acid secretion. The major mechanism utilized for adjusting the transport rate in both acute and chronic states is up- or downregulation of the H^+-ATPase and anion exchangers (AE1 in α-intercalated and pendrin in β-intercalated cells) inserted into the apical and basolateral membranes. Long-term adaptation utilizes this same response in addition to changes in the overall expression level of these transporters and, at some yet-to-be-quantitated rate, the interconversion of α- and β-intercalated cells.

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IgG4-related tubulointerstitial nephritis

Lynn D. Cornell[1]

Tubulointerstitial nephritis (TIN) is a disease pattern with heterogeneous causes. Recently a specific subtype of autoimmune TIN, IgG4-related TIN, has been identified that is part of systemic IgG4-related disease/autoimmune pancreatitis. On biopsy, this TIN shows an $IgG4^+$ plasma cell-rich infiltrate, akin to the pancreatic tissue findings in autoimmune pancreatitis, and may show tubulointerstitial immune complex deposits. Notably, some cases may be mass-forming. Recognition of this specific type of TIN can guide appropriate patient therapy.

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In 1961, Sarles *et al.* first described an entity of sclerosing pancreatitis with hypergammaglobulinemia and hypothesized that this entity was an autoimmune phenomenon.[1] Since then, this disease has been recognized as being related to increased IgG4, both as elevated levels of IgG4 in patient serum and in tissue sections with increased $IgG4^+$ plasma cells. In the past few years, the extrapancreatic features of 'autoimmune pancreatitis' (AIP) have been recognized,[2] thus calling for a new name for the disease. Now, IgG4-related systemic disease has been described in nearly every organ and organ system, first recognized in the pancreas, and then recognized in the liver, gallbladder, other gastrointestinal sites (sometimes including inflammatory bowel disease), salivary or lacrimal glands, lung, breast, retroperitoneum, lymph nodes, pituitary gland, prostate, and aorta.

The entity of IgG4-related systemic disease, while enjoying increased attention in the literature, has been largely unrecognized in regular clinical practice, especially when it affects organs outside of the pancreas. This disease is even more likely to be undiagnosed in the kidney, when renal biopsies of IgG4-related disease are diagnosed simply as tubulointerstitial nephritis (TIN) without a more specific diagnosis indicating the underlying cause of this disease pattern. As with glomerular diseases, which are, for the most part, specific and well defined in terms of histologic, ultrastructural, and immunophenotypic features, pathologists and clinicians should strive to identify and describe tubulointerstitial diseases in the same manner, with clinicopathologic correlation. TIN may be

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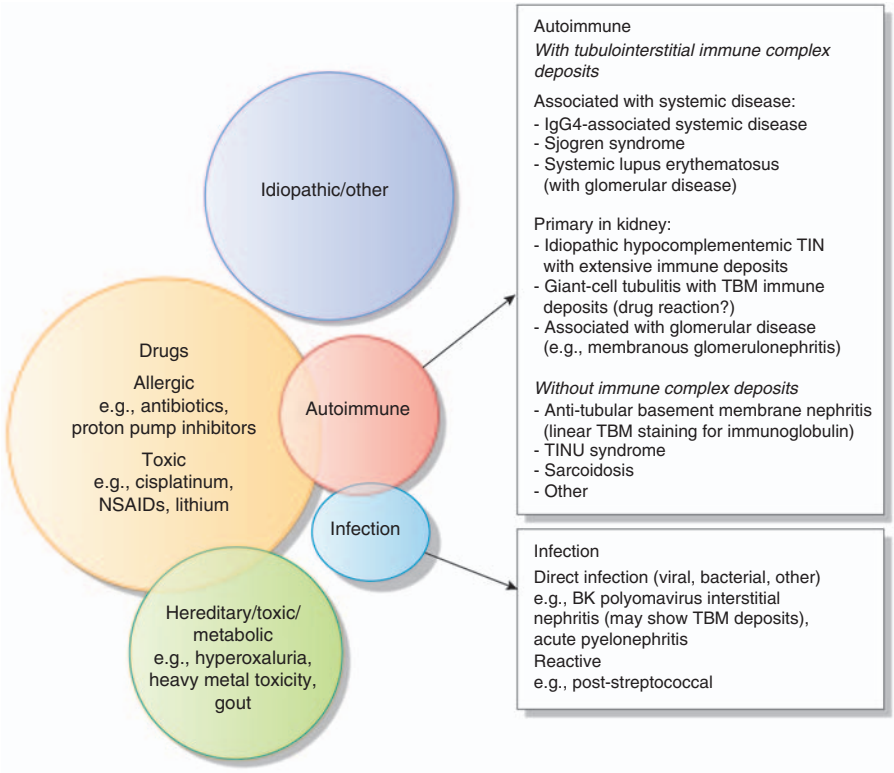

Figure 1 | Classification of tubulointerstitial nephritis/nephropathy. Tubulointerstitial nephritis/nephropathy cases can be placed into different etiologic categories, with the approximate relative prevalence on renal biopsy represented here by the size of each bubble. Tubulointerstitial nephritis (TIN) associated with systemic IgG4-related disease is an autoimmune TIN that usually has tubular basement membrane (TBM) and interstitial immune complex deposits. TBM deposits are an unusual feature in the absence of glomerular immune deposits, and their presence can help categorize a TIN. Sometimes overlap between etiologic categories exists: for example, some cases of BK polyomavirus infection show TBM immune complex deposits that stain for IgG and C4d, which may indicate an additional autoimmune reaction; and some cases of methicillin-induced TIN have anti-TBM antibodies. NSAID, nonsteroidal anti-inflammatory drug; TINU, tubulointerstitial nephritis with uveitis.

immunologically mediated, associated with drugs (allergic or toxic), associated with infection (either by direct infection or in reaction to a distant infection), hereditary, or metabolic or may be due to other causes (Figure 1). Overlap between categories is sometimes seen. TIN may also be a primary disease or may be associated with systemic disease. Recognition of the specific type of TIN then guides appropriate patient therapy.

Saeki *et al.*[3] (this issue), in a multicenter study, describe the largest histopathologic series to date of renal parenchymal involvement by IgG4-related disease. From a group of 153 patients with suspected IgG4-related systemic disease, approximately 20% had evidence of renal parenchymal disease, including radiographic abnormalities, abnormal urinalysis, or renal dysfunction. This percentage is similar to that seen in radiographic studies demonstrating 30% of patients with AIP as having renal parenchymal involvement.[4] The predominant feature in 23 patients whose renal tissue was examined was TIN, with characteristic histologic features of a plasma cell-rich infiltrate with a significant number of eosinophils in some cases. IgG4 immunostaining revealed at least a moderate amount of $IgG4^+$ plasma cells in all cases. Furthermore, all of the 22 patients with a measurement had an elevated serum IgG4 level, and the other patient had an elevated serum total IgG level. Nearly all of the patients included in the study had some form of extrarenal involvement by this autoimmune disease, notably 13 of 23 without a diagnosis of (pancreatic) AIP.

The study by Saeki *et al.*[3] draws attention to and further defines this specific type of TIN. The presence of a plasma cell-rich TIN in a patient with a renal mass or enlarged kidneys on imaging studies, hypergammaglobulinemia, hypocomplementemia, or a history of an extrarenal inflammatory mass should alert the pathologist to consider this entity, and perhaps to perform IgG4 immunostaining. Although not specifically studied by Saeki *et al.*, tubular basement membrane immune complex deposition is a helpful feature to suggest an autoimmune etiology of TIN and may show IgG4-dominant staining in cases of IgG4-related TIN.[5]

How useful is IgG4 immunostaining in cases of TIN? In the pancreas, a moderate to marked increase in $IgG4^+$ plasma cells (usually defined as at least 10 cells per high-power field in the most dense areas) is one of the diagnostic criteria for AIP.[6] In one study, although such an increase was diagnostically helpful when present, only 72% of AIP patients had at least moderately increased $IgG4^+$ plasma cells in pancreatic specimens.[6] This finding correlates with other studies that show elevated serum IgG4 in only about 70% of patients. Elevated serum IgG4 levels and tissue $IgG4^+$ plasma cells tend to occur together.[7] Certainly, IgG4 immunostaining is useful in supporting an etiologic link between AIP and its extrapancreatic involvement in the kidney. The diagnostic specificity of IgG4 staining in the kidney is unknown, however, and so the pathologist cannot rely on this one test to make the diagnosis.

Furthermore, in the study by Saeki *et al.*,[3] patients were selected for inclusion on the basis of having increased IgG4 in tissue or in the serum, and so those potential patients with 'low-IgG4' AIP-associated disease were necessarily excluded. Extrapolating from the pancreatic literature, 'low-IgG4' TIN associated with a systemic autoimmune disease may affect up to 30% of these TIN cases. Definition of 'low-IgG4' autoimmune TIN, therefore, remains an open question.

A few scattered case reports exist of glomerular disease in IgG4-related systemic disease, mostly reports of membranous glomerulonephritis (MGN). This largest series of IgG4-related TIN includes two cases of MGN (~9% of the cases), along with one case of IgA nephropathy, and

three cases of other (undefined) glomerular disease. MGN as a potential etiologic link with IgG4-related systemic disease is intriguing because idiopathic MGN is also an IgG4-dominant disease, such that these may have a common pathogenetic link.

IgG4 itself is an unusual antibody and has some unusual physical characteristics. It is the rarest IgG subclass in the circulation of normal individuals. Elevated titers of IgG4 are found in conditions of chronic antigen exposure; beekeepers, for example, show elevated IgG4 directed against bee venom, and patients undergoing allergen immunotherapy develop increased IgG4 titers against the allergen. Compared with IgG1, the IgG4 molecule has weaker interchain disulfide bridges, so that immunoglobulin half-molecules, composed of one heavy chain and one light chain, dissociate from each other. Once these dissociate, an IgG4 half-molecule may reassociate with another half-molecule with specificity for a different antigen.[7,8] When IgG4 encounters antigen, it can only form small, and presumably harmless, immune complexes and may block antigen binding by the more pathogenic IgG1. IgG4 is also unable to fix complement. In these ways, IgG4 is thought to act as an anti-inflammatory molecule that can temper the immune response, at least in some circumstances.

While IgG4 is an 'anti-inflammatory' immunoglobulin, it is perplexing that it is found to be increased in some disease states, most notably IgG4-related systemic disease. The mechanism of this disease and its association with IgG4 is unclear. IgG4 class switching depends on interleukin-4 and/or interleukin-13 mainly secreted by T-helper 2 cells. These are the same cytokines that promote an IgE response, although IgG4 antibody may be present in the absence of IgE antibody against a particular antigen. Interleukin-10 (IL-10) has an effect on IgG4 versus IgE class switching[9] and may be required for IgG4 class-switched B cells to differentiate into IgG4-secreting plasma cells. One may speculate that, in IgG4-related systemic disease, an initial insult and process involving production of anti-inflammatory cytokines, including IL-10 and tumor necrosis factor- α, along with fibrogenic IL-13, drives increased fibrosis, induction of IgG4 class-switched B cells, and production and massive expansion of IgG4-secreting plasma cells.

TIN is a disease pattern with heterogeneous causes, both immune and nonimmune. The clinical presentation, laboratory results, and biopsy features are all considered to make a specific diagnosis. Through the work of Saeki *et al.*,[3] we now have a clearer view of the clinicopathologic features of a specific type of TIN that is part of systemic IgG4-related disease, which in turn will aid pathologists and clinicians in recognizing and offering appropriate treatment for this disease.

DISCLOSURE
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Parathyroid resistance to FGF23 in kidney transplant recipients: back to the past or ahead to the future?

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Fibroblast growth factor 23 (FGF23) modulates the metabolism of minerals and vitamin D. In chronic kidney disease (CKD), this process is disturbed owing to decreased parathyroid expression of FGF23's receptor complex Klotho-FGF receptor 1. In this issue, Krajisnik and colleagues demonstrate that similar alterations occur in parathyroid glands from kidney transplant recipients in association with a decline in allograft function. Is it possible that these data can be extrapolated to general early-stage CKD patients?

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Within the past few years, it has become apparent that fibroblastic growth factor 23 (FGF23), a bone-derived phosphaturic hormone, plays a central role in the physiological regulation of mineral and vitamin D metabolism. FGF23 induces urinary phosphate excretion by suppressing the expression of the sodium-phosphate cotransporter. FGF23 also suppresses the synthesis of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] via inhibition of 1α-hydroxylase and stimulation of 24-hydroxylase.[1] These effects are dependent on the presence of Klotho, which converts

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