Acute Lobular (Membranoproliferative) Glomerulonephritis with Hyperuricemia and Obstructive Uric Acid Nephropathy

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ABSTRACT

Allen, Arthur C.: Acute lobular (membranoproliferative) glomerulonephritis with hyperuricemia and obstructive uric acid nephropathy. Am J Clin Pathol 65: 109-120, 1976. Obstructive uric acid nephropathy, a potentially lethal complication of acute renal failure due to glomerulonephritis, is described and illustrated. The factors leading to its occurrence and the reasons it may be undetected are detailed. Lobular glomerulonephritis is also briefly defined once again. (Key words: Lobular glomerulonephritis; membranoproliferative glomerulonephritis; Hyperuricemia; Obstructive nephropathy.)

THE HIATUSES in our knowledge of the complex interplay between hyperuricemia and such modifying renal vectors as glomerular filtration, tubular reabsorption, secretion, possibly with tubular biosynthesis, are appreciable and have attracted intensified investigative interest in the past year or two. What were once considered facts of urate homeostasis—even in health, but surely in disease—are now within the realm of speculation, as Rieselbach and Steele15 disarmingly disclose. Not the least puzzling is the common disparity between the level of uricemia and the deposition of crystals within renal tubules, as well as the reasons for the deposition of urate crystals in some instances and uric acid in others. The latter aspect has generally been neglected, as may be judged by the frequently imprecise use of “urates” for “uric acid” in the references to the crystals. Observations on the intrarenal precipitation of crystals of both urates and uric acid have been limited largely to their normal, albeit inadequately studied, occurrence in newborn infants and to patients with primary gout and malignant lymphomas. Gout secondary to chronic plumbism, sarcoidosis, psoriasis, Wilson's disease and chronic renal failure, especially that due to polycystic disease, has also attracted some attention. This communication is concerned with the occurrence of massive, obstructive, intratubular deposits of uric acid crystals in acute renal failure associated with hyperuricemia secondary to acute lobular (membranoproliferative) glomerulonephritis. It is suggested that this conjoint dysfunction embodies one small aspect of the overall, incompletely resolved problems of renal urate homeostasis. It is further suggested that obstructive uric acid nephropathy in acute renal failure is more common than is generally appreciated and may be overlooked, for reasons outlined below.
Report of a Case

A 23-year-old Caucasian man was transferred to our hospital from another institution for investigation and treatment of oliguria and azotemia of several days' duration. Relevant history dated back to the age of 9 years, when the patient experienced a sore throat followed seven to ten days later by fleeting articular pain and swelling. A diagnosis of rheumatic fever was made. Subsequently he was found to have a cardiac murmur and was placed on a prophylactic regimen of penicillin therapy, which he followed faithfully until the present illness.

During the interval, exertional dyspnea and moderate orthopnea developed. Approximately two months prior to hospitalization, the patient was scheduled to be digitalized, but he neglected to take the digitalis as prescribed. Four weeks later, there was a noticeable increase in dyspnea, accompanied by cough and low-grade fever. His acute illness was diagnosed as bronchopneumonia, which was treated with unspecified antibiotics. The cough and fever gradually cleared. However, the exertional dyspnea became more noticeable and was associated with cough and low-grade fever. His acute illness was diagnosed as bronchopneumonia, which was treated with unspecified antibiotics. The cough and fever gradually cleared. However, the exertional dyspnea became more noticeable and was associated with abdominal and pedal swelling, for which he was admitted to the initial hospital. At this time the temperature was 100.2°F., pulses were regular, and blood pressure readings ranged from 170/80 to 170/10 mm. Hg. The heart was markedly enlarged, and a blowing systolic murmur was detected in the mitral area. Crepitant rales were heard at both bases. The edge of the liver was 5 cm. below the right costal margin. Ascites was suggested by a fluid wave, and 2+ pretibial edema was present.

Roentgenogram of the chest revealed cardiac enlargement on both the left and the right, straightening of the left cardiac border, and a double density along the right. An electrocardiogram showed regular sinus rhythm, P-wave abnormalities, no axis deviation, and nonspecific ST-T-wave changes.

The blood count on that admission disclosed: hemoglobin 15.2 Gm. per 100 ml., hematocrit 46%, leukocyte count 10,800 per cu. mm., with a normal differential. Urinalysis showed a "smoky" urine with a specific gravity of 1.017, protein ++, 3-5 leukocytes and 75-100 erythrocytes per high-power field. Blood glucose was 98 mg. per 100 ml., urea nitrogen 92 mg. per 100 ml., serum albumin 3.7 and globulin 1.4 Gm. per 100 ml. The serology was negative. On the following day, the results of urinalysis were essentially the same. Urea nitrogen concentrations ranged from 124 to 150 mg. per 100 ml.; serum creatinine, from 8.5 to 10.2 mg. per 100 ml.; serum uric acid was 19.6 mg. per 100 ml. CO₂ 17.5 mEq. per L., chlorides 92 mEq. per L., sodium 133 mEq. per L., and potassium 5.1 mEq. per L. SGOT was 216 units and LDH, 780 units. Potassium, sodium and CO₂ were essentially unchanged from the previously recorded levels.

The patient became afebrile and was treated with 0.2 mg. digitoxin daily. Mercuhydrin (2 ml., intramuscularly) was given on admission, along with 40 mg. Lasix orally for three days with an additional 60 mg. intravenously on the third day. Ampicillin (250 mg., q.i.d.) was started on the second day and continued until the patient's transfer the following day. Glucose (5%) in water (1,000 ml.) was given intravenously. Thiazides or salicylates were not prescribed. This time the urinary output was described as oliguric, at which point the patient was transferred to our hospital with a diagnosis of acute renal failure. His temperature was 98°F., pulse rate 84 per min. and "water-hammer" in type, respiratory rate 22 per min., and blood pressure 160/10 mm. Hg. Grade I–II hypertensive retinopathy was present. The neck veins were distended at 30 degrees. The lungs were essentially clear. Aortic diastolic and systolic and mitral systolic murmurs were heard. The liver was palpable 6 cm. below the right
costal margin and 4+ ankle edema was present.

An electrocardiogram was described as showing evidence of hyperkalemia. Blood chemistry values included: blood urea nitrogen 143 mg. per 100 ml.; CO$_2$ 10 mEq. per l.; chloride 75, sodium 122, and potassium 6.7 mEq. per l. Peritoneal dialysis was begun, and the following morning a negative fluid balance of 1,150 ml. was recorded. The EKG continued to show peaked T waves. Laboratory studies on the following day revealed blood glucose 170 mg. per 100 ml., blood urea nitrogen 140 mg. per 100 ml., creatinine 10.8 mg. per 100 ml.; CO$_2$ 16, chloride 84, sodium 129, potassium 4.8. mEq. per l.; calcium 8.3 mg. per 100 ml., phosphorus 12.3 mg. per 100 ml. cholesterol 156 mg per 100 ml., and SGOT 36 units. Prothrombin time was 21.9 seconds, with a control of 13.9. A blood culture was sterile. Urinalysis showed a specific gravity of 1.012, with many erythrocytes and leukocytes. No casts were seen, but the presence of many uric acid crystals was recorded. A profile of serum complement was not determined.

Corrigan pulses, a harsh decrescendo murmur at Erb’s point, an S$_3$ gallop, and a rumble at the apex were recorded. A pleuropericardial rub was present in the aortic area. The blood pressure at this time was 200/0 mm. Hg. Bilateral pretibial edema persisted. Peritoneal dialysis was stopped after 50 hours, at which time the patient had lost 5,525 ml. of fluid. During his final fourth day in the hospital, the patient was restless, walked to the bathroom and, on returning to his bed, became apneic and failed to respond to cardioresuscitative measures.

Necropsy

Gross. The body was that of a 5’7” well-developed and well-nourished 23-year-old Caucasian man weighing 64 kg. The lower extremities showed 4+ pitting edema. No icterus or uremic frost was present. There were approximately 200 ml. of clear fluid in the abdominal cavity, but the pericardial and pleural cavities were free of fluid, exudate and adhesions.

The positive findings pertained to the heart, liver and kidneys. The heart was markedly enlarged weighing, 950 Gm. The epicardial surfaces were smooth and glistening. The chambers were all moderately dilated and the walls, particularly that of the left ventricle, hypertrophic. The annulus of the posterior mitral leaflet was focally calcified without compromise of the lumen. Each of the aortic cusps was shortened, and their smooth free margins were thickened and rolled, by grayish white, fibrous tissue. Their commissures were distinctly separated, leaving them mainly insufficient as reflected by subvalvular insufficiency pockets in the ventricular endocardium of the outflow tract. There was no evidence of verrucae or vegetations. The coronary arteries were unremarkable. The liver was extremely congested.

The kidneys were enlarged, the left kidney weighing 210 Gm. and the right, 200 Gm. Their structures were identical. They were of normal shape and their capsules stripped easily from smooth, purplish red surfaces. The sagittally cut sections showed the pelvis and calyces to be of normal size and shape and free of crystals. The cortices were grayish brown, thickened to 8 mm., and sharply demarcated from the medulla. The pyramids were congested but, in addition, were streaked by bright yellow lines converging toward the papillae (Figs. 1 and 2). These were noted, at the time of autopsy, to be strikingly reminiscent of the picture of uric acid “infarcts” commonly seen in the renal medullae of newborn infants.

Microscopic. The histologic appearances of the two kidneys were similar and showed the pattern characteristic of acute lobular glomerulonephritis. The glomeruli were diffusely enlarged owing both to dilatation of Bowman’s spaces and
FIG. 1 (upper). Gross photograph of the kidney, showing light-colored linear medullary streaks filled with uric acid crystals.

FIG. 2 (lower). Black columns consisting of masses of uric acid crystals and sludge within collecting tubules. Frozen section: hematoxylin and eosin. ×8.
Fig. 3 (upper, left). Acute lobular (membranoproliferative) glomerulonephritis. Hematoxylin and eosin. ×210.

Fig. 4 (upper, right). Acute lobular (membranoproliferative) glomerulonephritis. Chromotrope silver methenamine. ×420.

Fig. 5 (lower, left). Acute lobular (membranoproliferative) glomerulonephritis. Hematoxylin and eosin. ×210.

Fig. 6 (lower, right). Acute lobular (membranoproliferative) glomerulonephritis. PAS stain. ×210.
to proliferation of the elements of the malpighian tufts. The tufts generally assumed a lobular pattern, although in some the lobules were fused into hypercellular, hypervascular congeries (Figs. 3–6).

The predominant cells were endothelial and they occupied the centrilocular locations along with the cross sections of the basement membranes of the glomerular capillaries to which they belonged (Figs. 3–6). No crescents were present although, occasionally, synecchiae bound a portion of a lobule to Bowman’s capsule or to another lobule. Polymorphonuclear leukocytes were absent. The membranes of the glomerular capillaries were only minimally thickened (Figs. 3–6). No glomerular sclerosis was present. The PAS and the chromotrope silver methenamine stains served to reinforce the impression derived from the sections stained with hematoxylin and eosin (Figs. 4 and 6).

Bowman’s spaces, as indicated, were fairly uniformly dilated and contained much protein precipitate (Figs. 3 and 5). This dilatation reflects the obstruction and dilatation of the distal tubules. Bowman’s capsules were of normal thickness. However, often the parietal epithelial cells lining the capsule were focally thickened by granular cytoplasm similar to that of the proximal tubular cells.

The lumens of the proximal tubules were only minimally dilated and also contained a good deal of protein precipitate. Their epithelium was not altered except for traces of sudanophilic droplets. The striking tubular lesion was in the collecting tubules, which were packed with obstructing masses of intact or fragmented uric acid crystals, as noted particularly in frozen sections either unstained or stained with methylene blue or hematoxylin–eosin (Figs. 2, 8–10). The crystals were circular, averaged approximately 50 to 75 microns in diameter, and

characteristically showed radiating lines extending to doubly contoured circumferences (Figs. 10 and 11). A few were encrusted with calcium. Much intratubular crystalline debris was associated with the intact crystals; these reacted positively with the De Galantha stain (Figs. 7 and 9). Of special interest was the brilliant birefringence of both the uric acid crystals and uric acid sludge when examined in frozen sections (Figs. 10 and 11). The surfaces of many of the crystals were dotted with highlights, and under polarized light they appeared dappled with green, yellow, blue and orange in beautiful, kaleidoscopic patterns. The birefringence was partially or completely lost in sections processed for permanent mounts. In addition, the crystals were progressively and quickly depleted in formalin-fixed tissues until the bulk of them was gone and their landmarks were largely the dilated empty or almost empty tubules that once had contained them (Fig. 7). None of the crystals was within the interstitial tissue. As mentioned, the epithelium of the proximal tubules was not significantly modified. Furthermore, there was no remarkable alteration of the epithelium of the distal nephron beyond flattening due to compression and, occasionally, evidence of reaction apparently to irritative injury and proliferative regeneration. These were too sparse to have been of physiologic importance. There were no tubular (or interstitial) collections of acicular crystals of monosodium urate, nor were there any tophi or the giant-cell reactions usually associated with these crystals. There was no metastatic calcification. Bland, minimal interstitial edema was present in the cortices. There were no extraglomerular vascular changes of note.

The positive findings in other organs confirmed the diagnosis of rheumatic aortic valvulitis and passive hepatic congestion with marked, diffuse, hypoxic centrilobular necrosis. No giant-cell granulomas or crystals were present in these other organs.

**Anatomic Diagnoses.** Anatomic diagnoses were: lobular (acute, membranoprolifera-
tive) glomerulonephritis; obstructive uric acid nephropathy; chronic rheumatic aortic valvulitis with aortic insufficiency and marked cardiac enlargement; passive congestion of the liver with diffuse centrilobular hypoxic necrosis.

Lobular Glomerulonephritis

The term “lobular glomerulonephritis” was first applied in 1951 to the sclerotic lesion, previously and variously labelled by Bell, that pioneering renal morphologist as “chronic azotemic,” “hydropic,” “latent,” or simply “chronic” glomerulonephritis. Actually, our special interest in the problem dates back to 1941, when the histologic criteria were established for distinguishing this lesion in its chronic stage from diabetic glomerulosclerosis, with which it was commonly and continues to be confused. The additional purposes of that communication were to advance our insight to the pathophysiology of the proteinuria in the nephrotic syndrome and, above all, to correct the notion originally advanced by Kimmelstiel and Wilson that there was “only a difference in degree between the less marked changes frequently observed in senile kidneys” and the lesion later recognized as specific and called first “intramural” and then “diabetic glomerulosclerosis.”

An extended discussion of the histogenesis of lobular glomerulonephritis is not germane to this article, but mention will be made of the persistent misconstruction of what was initially and thereafter meant to be encompassed by the term. This lesion is now variously referred to also as “mesangiocapillary,” “mesangioproliferative,” “hypocomplementemic persistent” glomerulonephritis, “dense deposit disease,” and, more appropriately, “membranoproliferative glomerulonephritis.” A more vivid reflection of the prevalent confusion than even this terminology suggests is afforded by the discussion at a recent international symposium on the subject. With refreshing candor, admission is made, belatedly to be sure, that perhaps the prior, dogmatic pronouncements regarding the mesangial nature of the eosinophilic, centrilobular material merit re-examination.

As we indicated in several publications, lobular glomerulonephritis consisted not of a “simplification” of glomerular structure or of “mesangial” and “axial” proliferation but of a complex combination of alterations in the networks of centrilobularly located walls of the glomerular capillaries along with their attendant principally endothelial cells. The changes in the walls ranged from minimal thickening to a marked fibrinoid degeneration with progressive coalescence and eventual sclerotic obliteration of the lumens of the centrilobular capillaries. The spectrum of cellular changes varied from collections of polymorphonuclear leukocytes to conspicuous hyperplasia and hypertrophy of endothelial cells, which, as illustrated, were superimposed, in some instances, onto membranous glomerulonephritis. Accordingly, the stages of lobular glomerulonephritis may be acute, “subacute,” or chronic. The lesion forming the basis of this report may be classified as acute lobular (membranoproliferative) glomerulonephritis occurring in a patient with concomitant hyperuricemia, oliguria and acute renal failure.

The pursuit of the mesangial versus membranous disputation is, as just noted, a topical activity that may yet prove fruitful. In the meantime, it would seem worthwhile to redirect the polemics away from the metasemantics of lobular glomerulonephritis toward, say, the mechanisms of the hypertension and of the proteinuria that may accompany not only lobular glomerulonephritis but also diabetic glomerulosclerosis, which it resembles. Generally, these vital dysfunctions are relegated to the arcane or, as in the case of proteinuria, the mechanism is considered as credibly explained on the basis of an assumed although unlikely
FIG. 10 (upper, left). Crystals of uric acid within the lumens of collecting tubules. Lobular glomerulonephritis. Frozen section: hematoxylin and eosin. ×420.

FIG. 11 (upper, right) Field in Figure 10 under polarized light, showing the crystals characteristic of uric acid. ×420.

FIG. 12 (lower, left). Uric acid crystals within collecting tubules of a patient with treated acute lymphoblastic leukemia. Frozen section; hematoxylin and eosin. ×420.

FIG. 13 (lower, right) Uric acid crystals from a renal uric acid "infarct" of a newborn infant. Frozen section: methylene blue. ×420.
porosity of sclerotic "intercapillary," "axial," or "mesangial" tissue. This view is widely, if vaguely, held despite more tenable explanations, which, again, will not be repeated here.¹⁻⁴

Finally, as illustrated by this report, there is underscored an additional grave complication of acute renal failure, namely, the obstructive precipitation of crystals of uric acid. Although potentially serious, this dysfunction, too, has nonetheless failed to excite appropriate analysis. It is discussed further in the following paragraphs.

**Uric Acid Nephropathy**

Uric acid nephropathy with concomitant acute renal failure—at times, lethal—has become in recent years well known as a hazard in the chemotherapy of those myeloproliferative disorders in which massive amounts of free purine bases are cleaved from nucleosides and degraded into uric acid. Far less common are those instances of chronic renal failure with scattered deposits of sodium urate in the kidneys along with signs and symptoms of secondary gout. Our own experience with a fairly large sample of kidneys from patients in chronic renal failure due to nephrosclerosis, chronic pyelonephritis and chronic glomerulonephritis, with a possible single exception, has failed to disclose any with medullary tophi caused by crystals of monosodium urate in the proved absence of primary gout. On the other hand, in a careful study of 62 cases of chronic renal disease, Verger and associates found medullary tophi "with or without" crystals in 17.¹⁷ Although this is a remarkable disparity that needs to be clarified, the occurrence of signs and symptoms of secondary gout, as previously stated, is well documented in chronic renal disease with prolonged uric acid retention, particularly in such special situations as polycystic disease, psoriasis, sarcoidosis, Wilson’s disease, and, above all, chronic lead poisoning.

In any event, the crystals of concern in this present report are uric acid rather than monosodium urate monohydrate, and the associated lesions are acute lobular (membranoproliferative) glomerulonephritis with obstructive uric acid nephropathy. In other words, two lesions were present, either of which is capable of effecting acute renal insufficiency. There is adequate basis to attribute the hyperuricemia and the associated presence of tubular crystals of uric acid primarily to the glomerulonephritis. Nevertheless, several questions remain. Whereas in the myeloproliferative diseases, particularly acute lymphoblastic leukemia, the source and precipitation of massive amounts of crystals of uric acid from the supersaturated, acidified fluid in the collecting tubules is easily comprehended, the mechanism and apparent inconstancy of such precipitation in the acute renal failure due to glomerulonephritis are not altogether clear. First, it must be established straightaway that the masses of coalescent spheroidal or disk-shaped crystals seen in the current instance of glomerulonephritis match in every detail—amount, configuration, color, localization and lack of associated inflammatory reaction—the corresponding deposits in the kidneys of patients with treated lymphomas, as well as the undisputed uric acid "infarcts" of newborn infants (Figs. 10–13). Why, then, is this phenomenon of obstructive uric acid nephropathy as rare as it appears to be in hyperuricemic patients with acute renal failure due to glomerulonephritis?

The answer to this question may very well be that such uric acid nephropathies are more common than the records indicate. The reason seems to lie largely in the
failure of the pathologist to detect them in routine sections inasmuch as the uric acid crystals tend to dissolve in formalin and, perhaps, other processing solutions, with only a few remaining, often as isotropic shells the significance of which may be missed. Accordingly, unless frozen sections of the kidneys are examined at the time of autopsy, the amount, quality and location of the crystalline deposits will be misjudged. However, important clues to the prior presence of the clogging precipitates are the dilated tubules, especially in the medulla (Fig. 7). In addition, residual, single birefringent, at times calcified, spheroidal crystals within the distal convoluted tubules and occasionally in the proximal tubules and loops of Henle may remain. Some of these undissolved individual crystals are indistinguishable from those the author for many years has associated with the hepatorenal syndrome and labelled "leucine-like." They may indeed be uric acid, but it is of interest that the plasma levels of many amino acids are elevated in the presence of hyperuricemia. These "leucine-like" crystals have been summarily labelled "calcium oxalate" by many who compare them with the crystals found in abundance in the renal tubules of individuals following the ingestion of ethylene glycol. As a matter of fact, the sheaves of crystals deposited in renal tubules following intoxication with ethylene glycol, and known to be calcium oxalate, are morphologically easily distinguishable from the crystals of monosodium urate, uric acid and those designated "leucine-like." The possibility exists that the secondary calcific encrustation of the latter crystals may have misdirected conclusions from studies by microincineration. Moreover, what appears to have been overlooked is that the crystals of calcium oxalate secondary to ethylene glycol poisoning are deposited almost exclusively in the lumens of the proximal rather than the collecting tubules.3

Alterations in Tubular Function

In the attempt to account for the intratubular precipitation of uric acid, it is natural to search for aberrations in tubular function. This is so because the kinetic interplay between tubular reabsorption of uric acid—perhaps at pre- and post-secretory levels—and tubular secretion is paramount in renal urate homeostasis.15 If to these are added the selective impairment of the tubular production of ammonia from glutamine with consequent recycling of glutamine for hepatic conversion to surplus uric acid, then the imputation of the tubules becomes reasonable. However, in the current instance, if functional tubular derangements occurred, there are inadequate morphologic changes to which they may be attributed. The necrosis and regeneration of tubular epithelium are simply too sparse to account for major functional derangements. On the other hand, it is thoroughly understood that functional renal aberrations may take place without their being reflected histologically. In our case, there appears to have occurred what Gutman once called a "breach in the renal dike" that normally keeps the flood of filtered uric acid from overwhelming the excretory apparatus.9 Undoubtedly, conspiring to augment this concentration and precipitation of uric acid, unionized and insoluble at the low pH of medullary urine, was the dehydration with oliguria engendered or, at least, abetted by the peritoneal dialysis with a negative fluid balance of more than 5 liters.

Uric Acid Versus Urate Crystals

Another bothersome question concerns the reason for the deposition of uric acid crystals in the current case (and in treated
lymphomas), as opposed to the precipitation of the acicular, irritative crystals of monosodium urate monohydrate in the renal tubules in primary as well as in some instances of secondary gout. Not only has this problem pretty much escaped the attention of investigators but surprisingly often, as already mentioned, there is an inaccurate use of “uric acid” when “monosodium urate” is intended.

Inasmuch as there is no direct correlation between the occurrence of hyperuricemia and the deposition of crystals of urate or of uric acid, variable, local intratubular factors over and above the hyperuricemia must be suspect. These include altered glomerular filtration, the vectors in the supersaturation and consequent precipitation of uric acid, the proteinuria, the pH of the filtrate, and the concentration of sodium in the filtrate, especially in the collecting tubules. The latter appears to affect the solubilities of uric acid and monosodium urate in reciprocal fashion.13 Perhaps the recently described animal model of the gout kidney will lend itself to the investigation of these variables. This model is produced in rats fed potassium oxonate, which competes with uric acid for uricase. Crystals of uric acid alone in the renal medulla are described by some observers, and crystals of both uric acid and monosodium urate by others.18

Acknowledgments. The photographs were taken by Mr. Marvin Ehlin.

References

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